THE AMERICAN JOURNAL of HUMAN GENETICS

THE AMERICAN JOURNAL of HUMAN GENETICS

Edited by

LAURENCE H. SNYDER

in collaboration with

RAY C. ANDERSON
PAUL R. DAVID
PHILIP LEVINE
HORACE W. NORTON
WILLIAM J. SCHULL
JAMES N. SPUHLER

Volume 7
1955

Published Quarterly by
AMERICAN SOCIETY OF HUMAN GENETICS

AMERICAN SOCIETY OF HUMAN GENETICS

BOARD OF DIRECTORS, 1955

President
C. N. HERNDON, M.D.
Bowman Gray School of Medicine

President-Elect
S. C. REED, PH.D.
University of Minnesota

Vice-President
HAROLD CUMMINS, PH.D.
Tulane University

Secretary
D. C. RIFE, PH.D.
Ohio State University

Treasurer
W. E. HESTON, PH.D.
National Cancer Institute

R. C. ANDERSON, PH.D., M.D.
University of Minnesota

H. B. GLASS, PH.D.
Johns Hopkins University

A. G. STEINBERG, PH.D.
Childrens Cancer Research Foundation

HOWARD LEVENE, PH.D.
Columbia University

NORMA FORD WALKER, PH.D.
Hospital for Sick Children, Toronto, Canada

C. C. LI, PH.D.
University of Pittsburgh

President, 1953
C. P. OLIVER, PH.D.
University of Texas

President, 1954
J. V. NEEL, PH.D., M.D.
University of Michigan

Editor
L. H. SNYDER, SC.D.
University of Oklahoma

Copyright, 1955, by the
AMERICAN SOCIETY OF HUMAN GENETICS
All rights reserved

Printed at the WAVERLY PRESS, INC.
Mt. Royal & Guilford Aves.
Baltimore 2, Maryland

CONTENTS

VOL. 7, NO. 1. MARCH, 1955

On Some Pitfalls in Developing an Adequate Genetic Hypothesis ..... *James V. Neel* 1
Frequency and Types of Mental Retardation in Twins ... *Gordon Allen and Franz J. Kallmann* 15
Two Different Mutations of the X-Chromosome Causing Diabetes Insipidus ... *Hans Forssman* 21
A Pedigree of Aniridia with a Discussion of Germinal Mosaicism in Man
T. Edward Reed and Harold F. Falls 28
A New Syndrome of Anomalies in Mice and a Possible Human Counterpart
Walter C. Morgan, Jr. 39
Split-Hand with Unusual Complications ..... *John B. Graham and Carl E. Badgley* 44
Genetic Study of Microcephaly Based on Japanese Material
Taku Komai, Ken' Ichi Kishimoto and Yasunosuke Ozaki 51
Intra-Uterine Selection by the ABO Incompatibility of Mother and Foetus ..... *Ei Matsunaga* 66
Data on the Linkage of Ovalocytosis and Blood Groups
R. Fujii, W. C. Moloney and N. E. Morton 72
Comments on the Rate of Mutation to Chondrodystrophy in Man ..... *Herman M. Slatis* 76
Syndactyly of the Ring and Little Finger ..... *Ola Johnston and Vernon V. Kirby, Jr.* 80
Book Reviews 83
Bibliography of Human Genetics ..... *V. Rae Phelps* 87

VOL. 7, NO. 2, JUNE, 1955

Chromatographic Studies on Urinary Excretion Patterns in Monozygotic and Dizygotic Twins. I. Methods and Analysis
H. K. Berry, Th. Dobzhansky, S. M. Gartler, H. Levine and R. H. Osborne 93
Chromatographic Studies on Urinary Excretion Patterns in Monozygotic and Dizygotic Twins. II. Heritability of the Excretion Rates of Certain Substances
S. M. Gartler, Th. Dobzhansky and H. K. Berry 108
The Inheritance of Personality ..... *B. Cattell, D. B. Blewett and J. R. Beloff* 122
Some Problems in Maternal Age ..... *Robert S. Krooth* 147
Estimation of the Frequency of Partially Sex-Linked Genes in Man ..... *Katumi Tanaka* 163
Hand Prints and Handedness ..... *D. C. Rife* 170
The Use of Multi-Allele Genetic Characters in the Diagnosis of Twin Zygosity
H. E. Sutton, P. J. Clark and W. J. Schull 180
Primordial Dwarfism and Ectopia Lentis ..... *V. A. McKusick* 189
The Chances of Excluding Paternity by the MNS Blood Group System ..... *W. C. Boyd* 199
Sex-Linked Hereditary Deafness ..... *J. Sataloff, P. N. Pastore and E. Bloom* 201
A Study of Variations in the Frequency of Twin Births by Race and Socio-Economic Status
A. M. Lilienfeld and B. Pasamanick 204
Book Reviews 218
Letters to the Editor 221
Bibliography of Human Genetics ..... *V. Rae Phelps* 223

VOL. 7, NO. 3, SEPTEMBER 1955

Chances of Excluding Paternity by the Rh Blood Groups ..... *William C. Boyd* 229
A Genetic Study of Multiple Polyposis of the Colon (With an Appendix Deriving a Method of Estimating Relative Fitness) ..... *T. Edward Reed and James V. Neel* 236
Aspects of Genetics in Psychology ..... *Arne Trankell* 264
Sequential Tests for the Detection of Linkage ..... *Newton E. Morton* 277
Book Reviews 319

VOL. 7, NO. 4, DECEMBER 1955

The Use of the Fertilities of Affected Individuals and their Unaffected Sibs in the Estimation of Fitness ..... *Robert S. Krooth* 325
The Dynamics of Racial Intermixture in the American Negro: Some Anthropological Considerations ..... *D. F. Roberts* 361
On the Unlikelihood of Significant Admixture of Genes from the North American Indians in the Present Composition of the Negroes of the United States ..... *Bentley Glass* 368
Concentration of Gastric Carcinoma, Peptic Ulcer, and Cholecystitis in a Family Group *George W. Hagy* 386
Possible Genetic Carriers in the Spherophakia—Brachymorphia Syndrome *H. W. Kloepfer and J. W. Rosenthal* 398
The Incidence of Cousin Marriages in a West-Swedish Rural Community *J. A. Böök and C. E. Måwe* 426
Data on the Etiology of Acute Intussusception ..... *Brian MacMahon* 430
Book Reviews 439
Letters to the Editor 443
Bibliography of Human Genetics ..... *Rae Phelps Mericle* 447
Index to Volume 7 455

The American Journal of Human Genetics

Vol. 7 No. 1 *March 1955*

On Some Pitfalls in Developing an Adequate Genetic Hypothesis[1]

JAMES V. NEEL

Heredity Clinic, University of Michigan, Ann Arbor, Michigan

INTRODUCTION

IT WOULD be redundant in this company to extol the advantages of membership in the American Society of Human Genetics. There is, however, one advantage which did not occur to me until several months ago, an advantage which I dare say has not occurred to most of you. This is in connection with the Presidential Address. Many societies are most restrictive in this matter. The president of such a society, who if his society is at all active already has problems enough, is required in the space of forty minutes to develop some broad philosophical topic, or to review succinctly his lifetime of endeavor in his chosen field. Our Society, by what I am sure is careful design, has adopted an entirely different pattern, one which some in this audience will in turn take advantage of. Apparently the only requirement for our Presidential Address is that the speaker talk about some subject close to his heart at the moment. This has already resulted in a remarkable diversity in the Presidential Addresses presented before this Society. Tonight I expect to strike off in still another direction.

By way of introduction to my topic, I should like to draw attention once more to the truly sobering breadth of our field of interest, and the resultant heterogeneity of background among our membership. Everyone likes to feel that his particular interest in science comes closest to being the "key" discipline. In point of fact, there is of course no key discipline in our complexly integrated science today. Yet I submit that there is no aspect of human biology with more ramifications than the study of human heredity. Philosophy, sociology, psychology, anthropology, medicine—all have seen their conceptual framework profoundly affected in recent years by developments within the area represented by our Society. However, this very breadth creates for us serious methodological problems. Human genetics has and must continue to attract the interest of many not primarily trained as geneticists. And, in reverse, trained geneticists may be asked to deal with traits, an appreciation of which calls for an understanding of all the complexities of modern medicine or psychology. It is axiomatic, then, that many of us in our research will frequently be concerned with areas just at the fringe of our knowledge. Intimately familiar with the do's and don't's of investigation in a particular area, our problem of the moment

Received September 16, 1954.

[1] Presidential Address delivered at the seventh annual meeting of the American Society of Human Genetics at the University of Florida, Gainesville, Florida, September 7, 1954.

may lead us into strange fields. Tonight I would like to discuss with you some of the Scyllas and Charybdises which lie in wait for us as we seek to extend our knowledge of inheritance in man.

Let me at the outset make it clear that in presuming to address you concerning some pitfalls to be avoided, I speak, not from some high vantage point, but as one who has already personally explored a number of these pitfalls, and not from the outside looking in, but from the inside trying to climb out. Little that I have to say is new, but this will scarcely come as a disappointment to any of you, since new ideas in science are, after all, extremely rare and practically never encountered in presidential addresses. In a sense, this presentation may be considered a continuation of the discussion on problems and methods in human genetics sponsored last October by the Morphology and Genetics Study Section, National Institutes of Health, U. S. Public Health Service and the American Cancer Society.

Although there are many matters which could be discussed under the ambiguous title of this address, time permits us to take a hurried look at only four of the problems which the contemporary genetic literature would suggest commonly arise in attempts to develop an adequate genetic hypothesis. Incidentally, these problems are not unique to human genetics but perhaps are more obvious because of certain limitations on the extent to which we can manipulate our material.

1. HETEROGENEITY OF MATERIAL

People and opportunities being what they are, something less than complete freedom of choice plays a hand in the problems which each of us selects for investigation. Still and away, however, we all do enjoy a certain latitude in the kinds of questions with which we come to grips. If one is interested—as most of us are—in developing a satisfactory, unique, and consistent formal explanation for the role of genetic factors in the etiology of a particular trait, then in the present state of our knowledge one is well advised to exercise care in the selection of the trait for study. The more homogeneous the material, the greater the probability of a successful genetic analysis. How does one recognize homogeneity? This is perhaps best answered in a negative fashion. If one assembles cases of a somewhat loosely defined disease or trait of variable age of onset, concerning whose presence or absence competent authorities may disagree, and for which the basis is poorly understood, one is not likely to find oneself with a genetically homogeneous collection of material. Thus, such traits in man as musical ability, superior intelligence, hypertension, idiopathic rotoscoliosis of the spine, or neurasthenia can scarcely be expected to fit into any simple genetic schema. Let me make it clear that I am not suggesting that geneticists should display no interest in such traits, but rather that in approaching them there be a clear recognition of the methodological implications of their probable mixed nature.

Even with the most careful selection, one may still encounter a certain lack of genetic homogeneity in one's material. But while it may not be feasible to eliminate all heterogeneity, one so oriented can at least strive to reduce the picture to the point where genetic analysis leads to the recognition of several biologically meaningful subdivisions of the material at hand. In other words, once one has reduced the

heterogeneity to a certain point, the genetic approach may make it possible to complete the resolution. Two specific examples will help to make my point. The first concerns gargoylism. Herndon, Goodman, and David, in a paper which will appear in an early number of the American Journal of Human Genetics, and from which I am kindly permitted to quote, describe this variably expressed syndrome as follows: "Clinically the affected children present a grotesque appearance which is likened to that of the gargoyles seen on Gothic cathedrals, from which the term "gargoylism" is derived. There is moderate disproportionate dwarfism, the head being large with prominent forehead and plump face. The skull is often scaphocephalic or oxycephalic and hypertelorism is frequent. Kyphosis is usual and extension of the joints is often limited, frequently with a claw-like appearance of the broad hands. The liver and spleen are enlarged, and the abdomen protuberant. Mental deficiency is common and may vary from moron to imbecile levels. Corneal clouding, deafness, hypertrichosis, inguinal or umbilical hernia and recurrent otitis media are frequently described. Cardiovascular disease is often seen.... Radiologic examination discloses widespread skeletal abnormalities, with thickening of the skull, vertebral deformities and wide thick ribs. The bones of the extremities are short and thick with dense structure, and the proximal epiphyses of the humerus and femur are frequently deformed." The basic pathology is a metabolic disturbance, but whether this is of lipid or carbohydrate metabolism remains a moot point.

The familial nature of gargoylism was apparent from the early case reports, several authors mentioning recessive heredity as a possible explanation (e.g., Cockayne, 1936). In 1946 Njå described a pedigree typical of sex-linked heredity, and on the basis of this pedigree plus a survey of the literature, which revealed an excess of affected males over females, suggested the possibility of two genetic types of the disease, one due to autosomal recessive heredity and the other to sex-linked recessive heredity. Herndon, Goodman, and David have now compiled all the case reports they could locate in the literature, finding a very significant excess of males over females (167 ♂♂:79 ♀♀), with some pedigrees published since Njå's also almost certainly illustrating sex-linked recessive heredity. On the assumption that this excess of affected males is due to a mixture of two genetic types of disease, they calculate by a maximum likelihood approach that in approximately 65 per cent of the sibships containing one or more affected persons the disease is due to autosomal recessive heredity, and in the remaining 35 per cent to sex-linked recessive heredity.

Njå noted that in affected members of his pedigree, as well as in several other pedigrees in which only males were affected, the clouding of the cornea so frequently seen in this disease was lacking, and raised the possibility that the sex-linked variety differed phenotypically from the autosomal variety in this respect. Herndon et al. have now divided the accumulated material into three groups, group 1 consisting of all cases observed in sibships containing at least one affected female, and presumably due to autosomal heredity, group 3 consisting of 21 males observed in 7 families wherein the distribution was very suggestive of sex-linked heredity, and group 2 consisting of cases observed in sibships containing only affected males, with presumably both genetic types represented. The cases were then tabulated with respect to certain clinical characteristics of the disease. The results are shown in Table 1.

TABLE 1. THE OCCURENCE OF CERTAIN PHYSICAL FINDINGS IN GARGOYLISM IN RELATION TO THE PROBABLE MODE OF INHERITANCE OF THE DISEASE (AFTER HERNDON, GOODMAN, AND DAVID, IN PRESS). FURTHER EXPLANATION IN TEXT

Clinical Signs	Group I, Autosomal Recessive, 96 Cases		Group II, Mixed, 129 Cases		Group III, Sex-linked, 21 Cases	
	Number	%	Number	%	Number	%
1. Corneal clouding	78	81.3	64	49.6	0	0
2. Dwarfing	70	72.9	60	46.5	7	33.3
3. Deafness	5	5.2	22	17.1	9	42.9
4. Limited joint extension	86	89.6	115	89.2	14	66.7
5. Typical facies	83	86.5	104	80.6	18	85.7
6. Cranial deformity	81	84.4	122	94.6	20	95.2
7. Hepatosplenomegaly	70	72.9	93	72.1	17	80.9
8. Mental defect	68	70.8	97	75.2	11	52.4
9. Spinal deformity	66	68.8	99	76.7	6	28.6
10. Hernia	44	45.8	73	56.6	11	52.4
11. Short neck	44	45.8	56	43.4	10	47.6
12. Otitis media	32	33.3	51	39.5	8	38.1
13. Hypertrichosis	28	29.2	35	27.1	5	23.8
14. Enlarged sella turcica	21	21.9	45	34.9	4	19.1

Groups I, II and III show graded significant differences at the 1% level with respect to items 1, 2 and 3, but not with respect to items 4 through 14.

Corneal clouding, as Njå suggested, emerges as characteristic of the autosomally inherited type; in addition, deafness is only seldom seen in this group but encountered in 43 per cent of the presumably sex-linked group. Thus, the application of genetic techniques serves to sort out of a variably expressed syndrome several somewhat less variable subtypes, i.e., an apparent wide range of variability may be shown in some instances to be due at least in part to genetic heterogeneity.

Our own experience with sickle cell disease provides another illustration of how, where the heterogeneity of the data is not excessive, the genetic approach may actually help unravel that heterogeneity. The marked sickling tendency of the erythrocytes of certain persons, resulting in sickle cell disease, due as it is to the presence of an abnormal hemoglobin, would at first glance appear to be in all likelihood highly specific, genetically speaking, and such was our thought when we initiated our studies of this disease. But it now develops that although the bulk of sickle cell disease apparently does have a uniform genetic basis, being due to homozygosity for a particular gene, there are several additional, much less common, varieties, due to the combination of a single sickle cell gene with the genes responsible for thalassemia, hemoglobin C, or hemoglobin D. At this point the genetic approach makes a major contribution towards clarifying certain ambiguities in the sickle cell story. Recognition that a single sickle cell gene in combination with a thalassemia gene may produce sickle cell disease helps explain the observation that most of the reported cases of sickle cell disease in nominal Caucasians have occurred in individuals of Italian or Greek derivation, since the thalassemia gene has a relatively high frequency in such persons. Likewise, the recognition that the cases of sickle cell disease due to simultaneous heterozygosity for the sickle cell and hemoglobin C genes tend to be

mild helps explain the existence of apparent "intermediates" between the sickle cell trait and classical sickle cell disease (cf. Neel, 1952).

Even with the strictest possible adherence to a set of rigidly defined criteria, we may still encounter heterogeneity in our material. For instance, at last count there were known approximately a dozen different mutants of the shaker-waltzer variety in the house mouse, all inherited as if due to a single autosomal dominant or recessive gene (Grüneberg, 1952). Although some of these mutant strains are distinguished by associated morphological defects, such as syndactylism or coat color changes, and others by the precise behavior pattern of the animals and the course of the disease, there remains a number of strains distinguishable from one another only by genetic tests. In theory, in man a comparable situation could be analyzed in terms of the linkage relationships of the traits—but, as I have pointed out elsewhere (Neel, 1949), the difficulties in man of defining linkage relationships in single pedigrees are very considerable.

An even more striking example of genetic heterogeneity underlying phenotypic similarity is provided by the Tailless-Fused-Kinky mutants of the mouse. These rather similar phenotypes are due to mutation at three or more different loci, all contained within a chromosome segment having a maximum length of about eight cross-over units (Dunn and Caspari, 1945). One of these loci, Tailless, is apparently quite mutable, with some of the "mutations" suppressing crossing-over in immediately adjacent regions, this suggesting a chromosomal rearrangement (Dunn and Gluecksohn-Waelsch, 1953). Even the most enthusiastic student of human genetics must admit the inherent improbability of ever being able to analyze such a situation in man, and the consequent danger that our material is genetically heterogeneous.

Much of modern day genetic research, especially in the fields of psychology and medicine, is team research. This is sometimes a polite way of saying that someone with a collection of data suggesting genetic factors may be at work looks about for some genetic help. Who, now, examines the data from the standpoint of homogeneity? Let me register a strong vote for the geneticist. But, the latter may say, I really don't know that much about the condition in question. To that it can be replied that unless you have a good understanding of the traits involved, how do you decide the gauge at which to run your analysis? After all, one of the first rules of scientific procedure is not to carry third decimal places on data collected by rule of thumb.

It is perhaps relevant at this point to take cognizance of the fact that recently several distinguished scholars in our field have suggested that we may be approaching "the end of what can be accomplished by what we call the traditional, atomistic approach of working with . . . single gene substitutions" (Snyder, 1954; see also Dobzhansky and Wallace, 1954). I am of the opinion that this is the beginning rather than the end, that we are only now in a position to carry out many really basic studies on the physiology and population dynamics of these single genes, and that it would be premature to divert a large portion of our energies into studies of complex genetic situations before we have even begun to appreciate the lessons to be learned from intensive studies of single gene effects, lessons which by extrapolation may be of great value in approaching the more complex. Recent developments in

the field of hematological and serological genetics supply a number of reasons for that judgment (review in Neel, 1954). This point of view implies a continued apparent preoccupation with so-called pathological traits, a preoccupation which some might term undesirable, but it was just such a preoccupation as this that carried Drosophila genetics forward so fast.

In summary, then, it is suggested that there is no faster way to dull the edge of the beautiful mathematical tools which we now possess than to attempt to use these tools in inappropriate situations. A vast amount of work remains to be done on clearly defined traits involving "simple" one- and two-gene situations. From such work should come some of the insight we need for a successful attack on more complicated problems. In the meantime, we minimize the probability of future embarrassment—not to say actual opprobrium—by going no further than a statement as to heritability for many of the more complex traits. The conflict of opinion between such able investigators as Harris (1950) and Steinberg and Wilder (1952) on the genetics of diabetes mellitus, or Kallmann (1953) and Böök (1953) on the genetics of schizophrenia, probably arises primarily from the nature of their material; this conflict will persist until the data can be simplified.

2. PENETRANCE AND THE IMPROPER USE OF SECONDARY HYPOTHESES

The second point to be considered involves the improper use of secondary hypotheses. To no small extent, the strong intellectual appeal which the study of genetics holds for many of us stems from the opportunity to pursue a more precise and mathematical line of reasoning than is granted to most of our colleagues in biology. When studying the genetics of a particular trait, we commonly systematically test our data for agreement with one or several not improbable hypotheses. Recent years have witnessed an increasingly clear recognition of the extent to which such factors as a low level of ascertainment of the trait in the population, uncertainty of medical diagnosis, and a variable age of onset may distort fundamental ratios. These are now matters of common knowledge, which need scarcely be labored with an audience of this background.

There is, however, one problem which arises in the mathematical analysis of genetic data at which we shall take a rather critical look. Let us assume that we have carefully analyzed a set of data for agreement with monogenic or digenic heredity and we find, as is not too uncommonly the case with respect to many traits whose precise pathological basis is unclear, that there is a deficiency between observed and expected affected on each of several simple genetic hypotheses. At this point it is not at all uncommon to see the supplementary hypothesis of "incomplete penetrance" introduced. Thus, in recent years the familial pattern of such diseases as essential hypertension, bronchial asthma, paralysis agitans, rheumatoid arthritis, goiter, paralytic poliomyelitis, neurocirculatory asthenia, diabetes mellitus, and schizophrenia has been suggested to be consistent with monogenic heredity with incomplete penetrance. While some of these suggestions may be correct, others are almost certainly in error. Most geneticists reading the original papers will realize that while this is in one sense the simplest hypothesis, there are in each case several other quite tenable explanations. Unfortunately, the non-geneticist who peruses the

same paper scarcely can be expected to have acquired the background necessary to such judgments, and the sanctity of the printed word being what it is, the statement that such and such a disease is due to a single gene of incomplete penetrance soon becomes well seeded throughout the literature.

Under certain circumstances, as, for instance, in the case of the gene responsible for retinoblastoma, one can speak with considerable assurance of incomplete penetrance, amounting in this particular case to about 90 per cent. But as one descends the scale of penetrance, one arrives at a point, which we may arbitrarily place in the neighborhood of 60 to 70 per cent, where the extravagant use of the concept of incomplete penetrance, particularly in connection with the study of relatively common traits, creates in the end more problems than it solves. A scientifically productive hypothesis is one which suggests further manipulations of the data. The concept of incomplete penetrance seldom does so, since not only can almost any set of data be explained in terms of one gene and a "penetrance factor," but the concept so readily leads to a type of circular reasoning. Thus we say "the data are consistent with heredity due to a dominant gene with 70 per cent penetrance, therefore the gene probably has 70 per cent penetrance," and stop the analysis at this point. But as Stecher, Hersh, Solomon, and Wolpaw (1953) have recently demonstrated in a paper which illustrates the extremes to which the concept of penetrance can be carried, given a familial distribution of disease explicable as due to the effects of a dominant gene of incomplete penetrance, this situation can also often be "explained" by the postulate of dependence upon a recessive gene with a different degree of penetrance. Furthermore, the pedigree distribution of a trait due to the interaction of genes located at two or more loci may be very similar to the distribution of a trait due to an incompletely penetrant gene. On a priori grounds it is difficult to say that one of these possible explanations of a collection of data is more probable than the other, but distinguishing between the two may be mathematically impossible.

Where one is studying a trait in whose etiology genetic factors are important, and which has a variable age of onset, it is clear that one is justified in speaking of non-penetrance in individuals who have the necessary genetic background but are below the age of onset. Under these circumstances the term "non-penetrant" means only that we are unable to recognize any effect of the genetic background at that time. In this respect, it is like the term "recessive," which describes what the geneticist observes rather than any fundamental property of the gene. Continuing advances in our ability to recognize carrier states may increasingly relieve us from the necessity of falling back on the concept of non-penetrance. A case in point is supplied by recent work of Fajans and Conn (in press) on the prediction of susceptibility to diabetes mellitus. Certain individuals with a normal glucose tolerance curve develop an abnormal curve following small doses of cortisone. Among the siblings of diabetics (excluding, of course, those with manifest or occult diabetes), roughly a quarter show such abnormal responses, whereas only a few per cent of "normal" controls respond in this fashion. It is assumed that individuals exhibiting such abnormal responses have an increased risk of developing diabetes at some later date. We have been collaborating with Dr. Fajans and Dr. Conn on the genetic implications of this discovery, and find that when the familial pattern of both diabetes mellitus

and an abnormal response to cortisone is considered, the analytic problems involved in the study of heredity in diabetes may be considerably simplified.

It can confidently be anticipated that the future holds many similar discoveries with reference to genetically conditioned diseases, discoveries which it is to be hoped will minimize the need for the deus ex machina of non-penetrance. In the meantime, perhaps it is desirable in situations such as enumerated previously to speak of heritability in the broad sense rather than to attempt, prematurely, to specify a precise genetic mechanism which has a high probability of confusing the literature and haunting the author.

3. BIAS IN THE SELECTION OF CONTROLS

Thirdly, the matter of the selection and treatment of control material should be mentioned. Once the geneticist departs from the well blazed trail of one- and two-gene heredity and finds himself on the footpaths and backroads of "heritability" and "constitutional factors," the need for adequate controls asserts itself. The less clear-cut the genetics of a situation, the greater the need for adequate controls. In recent years we have seen several striking demonstrations of the manner in which the selection of controls alters the interpretation of one's findings. Time permits the discussion of only one example. In the past decade a number of very substantial studies on heredity in breast cancer have been carried out. Jacobsen (1946) compared the frequency of breast cancer in the relatives of 200 patients with this disease with its occurrence in the relatives of 200 controls with approximately the same age and, presumably, socio-economic distribution. A portion of his findings is reproduced in Table 2. The cancer percentages given in the table are the sum of the mortality from this cause among the deceased relatives in the designated category plus the morbidity among the living relatives in the same category. In very rough terms there appeared to be approximately ten times the amount of cancer in the relatives of the cancer probands than in the relatives of the controls. This is a striking difference. However, Busk (1948) pointed out that by comparison with official Danish mortality and morbidity statistics, there was a very significant deficiency of persons

TABLE 2. THE FREQUENCY OF CANCER OF THE BREAST IN (A) THE FEMALE RELATIVES OF 200 PATIENTS WITH CANCER OF THE BREAST (JACOBSEN), (B) THE FEMALE RELATIVES OF 200 CONTROL PATIENTS (JACOBSEN), AND (C) IN A HYPOTHETICAL CONTROL POPULATION BASED ON DANISH MORTALITY AND MORBIDITY DATA FOR BREAST CANCER (BUSK)

Relationship	Breast Cancer Relatives			Control Relatives			Hypothetical Control		
	Number	Affected	Per cent affected	Number	Affected	Per cent affected	Number	Affected	Per cent affected
Mother	200	21	10.5	200	2	1.0	200	4	2.0
Sister	381	13	3.4	433	2	0.5	433	2	0.5
Maternal grandmother	183	4	2.2	172	—	—	172	4	2.3
Paternal grandmother	157	4	2.5	162	2	1.2	162	4	2.5
Maternal aunt	316	17	5.4	312	—	—	312	5	1.6
Paternal aunt	224	12	5.4	223	2	0.9	233	4	1.7
Total	1461	71	4.9	1502	8	0.5	1502	23	1.5

TABLE 3. A COMPARISON OF THE OBSERVED AND EXPECTED FREQUENCY OF DEATH DUE TO MAMMARY AND NON-MAMMARY CANCER IN THE CLOSE RELATIVES OF WOMEN DYING BECAUSE OF MAMMARY CANCER (AFTER PENROSE, MACKENZIE, AND KARN, 1948)

Relative	Total No. of Deaths	A. Cancer Other Than Mammary		B. Mammary	
		Obs.	Exp.	Obs.	Exp.
Mother	406	51	49.23	25	11.12
Sister	307	19	25.23	23	6.97
Daughter	30	0	0.41	0	0.12
Father	420	41	52.32	0	0.10
Brother	455	29	28.14	1	0.05
Son	50	2	0.81	0	0.00
Total	1668	142	156.14	49	18.36
χ^2 (Obs.-Exp.)^2/Exp.		1.3		51.1	

with breast cancer among the controls, raising the strong suspicion that either the "controls" were non-representative of the general population or unfamiliar with the causes of death within their families. When Busk (1948) reanalyzed Jacobsen's data, using Danish vital statistics as control figures, the apparent increase in breast cancer among the mothers of such patients was reduced from ten-fold to three-fold.

Penrose, Mackenzie, and Karn (1948) investigated the frequency of cancer of the breast among the deceased relatives of 510 women with cancer of the breast. As a standard of comparison, they calculated the amount of cancer of the breast to be expected, on the basis of the official death certificates from England and Wales. The findings are shown in Table 3. There is good agreement between this study and Jacobsen's study as corrected by Busk. However, while this approach avoids the problems inherent in assembling controls—problems which have been eloquently enumerated by Macklin (1954; see also Dorn, 1954)—it assumes that the population studied is a miniature of the national population. While this assumption may be safe for areas with a relatively homogeneous population, the assumption would be unsafe in this country except for small and select areas.

Here in this country a number of important studies on familial factors in breast cancer have been carried out in recent years. Much of this material is still unpublished. Accordingly, in the course of preparing this paper, I wrote the principal architects of four of the studies—Dr. Madge Macklin, Dr. D. P. Murphy, Dr. C. P. Oliver, and Dr. Sheldon Reed—concerning the current status of their analyses. The response was most generous; I am extremely grateful to these investigators. In going over the results, one is impressed by two facts:

1) There is in general substantial agreement between these four studies, as well as the two already discussed, in indicating a two- to three-fold increase in the frequency of breast cancer among the mothers and sisters of breast cancer patients.

2) Certain real differences do appear to exist between the findings of the various studies—most notably between the results of Dr. Murphy and Dr. Macklin. I have no desire to inject myself gratuitously into a discussion of the cause of these differ-

ences, a discussion which has already enlivened several sessions of this Society. However, there are immediately apparent three possible explanations for the discrepancies between the various studies, namely, biological differences between the populations involved, procedural differences in the investigations, and differences in the statistical approach to the data. With respect to the latter, one of the basic issues involves the propriety of combining morbidity and mortality data into a single figure, wh n the various studies may well differ both as regards the relative contribution of t e two types of data and the age distribution of the individuals contributing to the data. Without expressing an opinion, I can perhaps voice the hope that the methods and data are presented in such a way that interested persons can judge for themselves the possible influence of various statistical treatments.

The point at issue in the present context is that the importance one ascribes to familial factors in the etiology of carcinoma of the breast is strongly influenced by the selection and treatment of controls. When the four largely unpublished studies mentioned earlier are published in detail, they, together with the earlier studies already mentioned, will provide an insight into the difficulties in assembling controls which should illuminate a good deal of future genetic investigation. Jacobsen was probably led to overemphasize familial factors in carcinoma of the breast because of under-reporting on the part of his control material. More recent studies, having gotten over this hurdle, are now facing a second, more statistical hurdle. Incidentally, in view of the recrudescence of interest in the possible viral etiology of various human malignancies (Gross, 1954), it should be pointed out that even if a virus were implicated in the causation of breast cancer, the observations of the above quoted studies would be in no way invalidated; the geneticist will be in trouble only if he prematurely places a precise genetic interpretation on a finding indicative only of familial factors.

4. FAILURE TO BEAR IN MIND THE UNIQUENESS OF MAN

Finally, there is need to mention the desirability of constantly bearing in mind the uniqueness of man. I must confess, as one who cut his genetical milk teeth on Drosophila, that there are times when I have fallen into the obvious trap of regarding man as an overgrown fruit fly. Others with different backgrounds perhaps see him as an enormous mouse. That this is not the case seems self-evident, and yet I wonder to what extent various of you here have shared this same pitfall with me. That we have learned a great deal from Drosophila and the mouse, there is no doubt, but perhaps the time has come for the flow of knowledge to be more of a two-way proposition.

Man is set apart from all other animals by the accumulation and transmission of a body of knowledge usually termed his culture, that is, by a cultural inheritance no less complex than his biological inheritance. In this culture, man is for what seem to be understandable reasons the pivotal figure, in consequence of which the available information concerning the human species far outstrips our knowledge of any other animal. The relationship which man's culture bears to our efforts to understand him has been explored in detail by many scholars (cf. Huxley, 1941; Simpson, 1949; White, 1949; Kroeber, 1952; Etkin, 1954). There is scarcely a single aspect of our attempts to study man which remains untouched by cultural factors. The uniqueness of man as an object of genetic study has been repeatedly impressed upon our group at Michi-

gan in connection with two of our major interests, namely, the study of human mutation rates, and the detection of genetic carriers of inherited disease. Scarcely a year passes but what some new facet of the differences between man and other animals as subjects for such investigation comes to light.

Consider, first, the study of mutation rates, a subject which Dr. Schull and I have recently reviewed in some detail elsewhere (Neel and Schull, 1954). It has been frequently pointed out that because of the impossibility of controlled matings in human societies, in most mutation rate studies on human material we cannot be sure that a given phenotype attributed to germinal mutation is not either a phenocopy, the result of somatic mutation, or due to complex recombination phenomena. The study on the rate of mutation of the gene responsible for retinoblastoma which Falls and I (1951) carried out some years ago may provide a good example of how this bias operates. Although recognizing the various alternative possibilities just mentioned, in the absence of actual data on the point, we were forced to assume for purposes of calculation that all sporadic cases of retinoblastoma were due to germinal mutation. Now, however, Nachtsheim (1954), in a paper prepared for the current World Population Conference, on the basis of data recently collected on the children of surviving, sporadic cases of retinoblastoma, raises the possibility that our estimate may be too high by as much as a factor of 4 because of the inclusion of phenocopies or cases due to somatic mutation in the mutation rate estimate. I very much doubt that the bias is as great as that, since the bilateral cases, which are most apt to be due to germinal mutation, have a lesser chance of survival than the unilateral, and, if they survive, a lesser change of reproduction. Nevertheless, here may be an excellent example of how this set of biases operates.

Furthermore, even if the phenotype under study is definitely due to germinal mutation, we cannot be sure that it does not result from change at any one of several different loci. Thus, even so apparently specific a disease as classical, sex-linked hemophilia is now a complex of at least two diseases, true hemophilia and plasma thromboplastin component (PTC) deficiency or Christmas disease, a fact that future mutation rate studies on this locus must bear in mind (cf. Symposium: What is Hemophilia? Blood 9: 244–293). It is obviously very unlikely that if some human mutation rate studies involve such compound loci as bithorax, Star, lozenge, vermilion, or white in Drosophila, we will ever be able to dissect the estimates down to their component parts. These facts will result in spuriously high estimates of human mutation rates.

But is it generally appreciated that there may be just as important biases operative in the other direction as regards the detection of mutation resulting in "visibles" (as opposed to lethals) in Drosophila? One of these is the small size of the organism, and the probability of overlooking departures from the norm which on an equivalent scale would be glaringly apparent in man. There is a second factor which has not been adequately stressed in the past. Most estimates of the frequency of mutation resulting in "visibles" in Drosophila are based upon the detection of single individuals showing the effects of sex-linked, recessive mutation, or sex-linked and autosomal dominant mutation. Some of the more refined estimates involve the search in suitably heterozygous strains for animals exhibiting the effects of autosomal recessive mutation. Save where gonadal mosaicism is involved, mutation of this type results in a single affected

individual. Now, many studies have demonstrated the impaired viability of most of the visible mutants of Drosophila. These demonstrations are usually based on departures from an expected 3:1 or 1:1 ratio. Viability may be even more impaired, relatively speaking, when the mutant is one among a culture of normal brothers and sisters. One can argue, then, that under the usual Drosophila culture conditions negative selection probably eliminates a very sizable fraction of mutant individuals before they ever come to the investigator's attention. So far as I am aware, no Drosophilist has ever performed the very simple experiment of introducing into scattered members of a series of wild type cultures of Drosophila, just as the flies are beginning to emerge, a single mutant fly, and seeing how many of these mutants are recovered by an unsuspecting but competent observer three days later. Contrast the situation in human populations, where the physician from the moment of birth is in constant attendance upon the ill and unusual.

Let us deal with equal brevity with the detection of genetic carriers in man (reviews in Neel, 1947, 1948; Falls, 1953; Franceschetti and Klein, 1954). In the final analysis, this is in large part the study of early, manifold, or subclinical gene effects. It has frequently been pointed out that such studies in man are complicated by our inability to standardize the genetic background. It is not commonly realized to what extent this is offset, again, by our extensive background information on man. A single recent example will make the point. Cystic fibrosis of the pancreas is a recessively inherited disease well known to the geneticist. Several years ago, during an unusually hot spell in New York City, it was first recognized that children with this disease are unusually prone to heat prostration (Kessler and Andersen, 1951). Later studies revealed an increased chloride loss in the sweat of such children, the proneness to heat prostration apparently being a consequence of sodium cloride depletion due to a congenital defect in the sweat glands (Darling, et al., 1953). Of even greater interest in the present context is the fact that among 60 close relatives, apparently for the most part parents and siblings, of children with the disease, distributed aong 18 families, 14 were found to have abnormally large amounts of electrolytes in their sweat (di Sant'Agnese, et al., 1954). These presumably are heterozygotes for the gene. From the proportion found to be abnormal, it does not appear that all heterozygotes exhibit the abnormality, but further studies, with more refined techniques, may reveal that the proportion of affected heterozygotes is higher than it appears to be at the present time. Here, then, is a new carrier state. Its recognition is the outgrowth of good clinical medicine plus an awareness of genetic principles. Let us assume a similar disease existed in some laboratory animal. I wonder how rapidly, granting that a susceptibility to heat prostration was recognized, its mechanism could be analyzed. The fact is that there is available to those of us interested in human genetics a richness of ancillary biological techniques which is available for no other living organism.

CONCLUDING REMARKS

Today geneticists are operating on a broad front indeed. At this very moment some members of this Society are participating in Section B-10 at the World Population Conference in Rome. Earlier in the year under UNESCO sponsorship a group which included geneticists met in Paris to try to come to grips with the implications

of differential fertility for the intelligence of future generations. Next month the annual Teaching Institute of the Association of American Medical Colleges will be devoted to the subjects of pathology, microbiology, and genetics. This is undoubtedly the most significant opportunity which has yet developed to present the place of genetics in the modern scheme of medical education. The burden of this presentation will again fall on members of this Society. Less specific but nonetheless tangible evidence of the breadth of our horizons comes from the still active controversy surrounding the subject of heredity in Russia, and the recent Papal statement devoted to the same subject.

As our external relations with other disciplines multiply, we will be tested on an ever-broadening scale. Mindful of the set-backs the study of human heredity has suffered in the past because of an uncritical approach to problems as profound as any with which man has ever grappled, it is imperative that in our present sturdy growth we constantly bear in mind these lessons. All of the pitfalls I have touched upon this evening have been adequately discussed by others in the past. They will bear reiteration in the future. May I suggest, as the "stop, look, and listen" of our discipline, the following four questions: Is my material as homogeneous as it can be made in the light of present knowledge? Have I considered exhaustively the various genetic hypotheses applicable to the situation under study? Where controls are indicated, have they been assembled by the best sampling methods available? And finally, have I been led to specious or unwarranted conclusions by thinking in terms of non-human material?

REFERENCES

Böök, J. A. 1953. A genetic and neuropsychiatric investigation of a north-Swedish population. *Acta Genet. et Stat. Med.*, 4: 1–100, 133–139, 345–414.

Busk, Th. 1948. Some observations on heredity in breast cancer and leukemia. *Ann. Eug.*, 14: 213–229.

Cockayne, E. A. 1936. Gargoylism (chondro-osteo-dystrophy, hepatosplenomegaly, deafness) in two brothers. *Proc. Roy. Soc. Med.*, 30: 104–107.

Darling, R. C., di Sant'Agnese, P. A., Perera, G. A., and Andersen, D. H. 1953. Electrolyte abnormalities of the sweat in fibrocystic disease of the pancreas. *Am. J. Med. Sci.*, 225: 67–70.

Dobzhansky, T., and Wallace, B. 1954. The problem of adaptive differences in human populations. *Am. J. Human Genet.*, 6: 199–207.

Dunn, L. C., and Gluecksohn-Waelsch, S. 1953. Genetic analysis of seven newly discovered mutant alleles at locus T in the house mouse. *Genetics*, 38: 261–271.

Dunn, L. C., and Caspari, E. 1945. A case of neighboring loci with similar effects. *Genetics*, 30: 543–568.

Dorn, H. F. 1954. Some problems in sampling human populations. *Statistics and Mathematics in Biology* (Kempthorne et al., eds.). Ames: Iowa University Press. pp. 241–249.

Etkin, W. 1954. Social behavior and the evolution of man's mental faculties. *Amer. Nat.*, 88: 129–142.

Fajans, S., and Conn, J. W. In press. An approach to the prediction of diabetes mellitus by means of a cortisone-glucose tolerance test. *Diabetes*.

Falls, H. F. 1953. Clinical detection of the genetic carrier state in ophthalmic pathology. *Tr. Am. Acad. Ophth. and Otolar.*, 57: 858–872.

Falls, H. F., and Neel, J. V. 1951. Genetics of retinoblastoma. *Arch. Ophth.*, 46: 367–389.

Franceschetti, A., and Klein, D. 1954. Le dépistage des hétérozygotes. *Analecta Genetica*, 1: 50–78.

GROSS, L. 1954. Is leukemia caused by a transmissible virus? A working hypothesis. *Blood*, 9: 557–573.

GRUNEBERG, H. 1952. *The Genetics of the Mouse.* The Hague: M. Nijhoff, 2nd ed., 650 pp.

HARRIS, H. 1950. The familial distribution of diabetes mellitus: a study of the relatives of 1241 diabetic propositi. *Ann. Eug.*, 15: 95–119.

HERNDON, C. N., GOODMAN, H. O., AND DAVID, P. R. Differentiation of the autosomal recessive and sex-linked forms of gargoylism. *Am. J. Human Genet.*, in press.

HUXLEY, J. 1941. *Man Stands Alone.* New York: Harper and Bros. x and 297 pp.

JACOBSEN, O. 1947. Heredity in breast cancer. *Opera ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis.* Vol. 11, Copenhagen: E. Munksgaard., 306 pp.

KALLMANN, F. J. 1953. *Heredity in Health and Mental Disorder.* New York: W. W. Norton and Co., 315 pp.

KESSLER, W. R., AND ANDERSEN, D. H. 1951. Heat prostration in fibrocystic disease of the pancreas and other conditions. *Pediatrics*, 8: 648–656.

KROEBER, A. L. 1952. *The Nature of Culture.* Chicago: University of Chicago Press, 438 pp.

NACHTSHEIM, H. In press. Mutationsrate und mutagene Faktoren, Selektionsdreick und Kontraselektion in ihrer Wirkung auf Frequenz und Verbreitung krankhafter Gene in wenschlichen Populationen. *Proc. World Pop. Conf.*, Rome.

NEEL, JAMES V. 1947. The clinical detection of the genetic carriers of inherited disease. *Medicine*, 26: 115–153.

NEEL, J. V. 1949. The detection of the genetic carriers of hereditary disease. *Am. J. Human Genet.*, 1: 19–36.

NEEL, J. V. 1952. Perspectives in the genetics of sickle cell disease. *Blood*, 7: 467–471.

NEEL, J. V. 1954 Implications of some recent developments in hematological and serological genetics. *Am. J. Human Genet.*, 6: 208–223.

NEEL, J. V., AND SCHULL, W. J. 1954. *Human Heredity.* Chicago: University Press. 361 pp.

NJÅ, A. 1946. A sex-linked type of gargoylism. *Acta pediat.*, 33: 267–286.

PENROSE, L. S., MACKENZIE, H. J., AND KARN, M. N. 1948. A genetical study of human mammary cancer. *Ann. Eug.*, 14: 234–266.

DI SANT'AGNESE, P. A., DARLING, R. C., PERERA, G. A., AND SHEA, E. 1953. Sweat electrolyte disturbances associated with childhood pancreatic disease. *Am. J. Med.*, 15: 777–784.

SIMPSON, G. G. 1949. *The Meaning of Evolution.* New Haven: Yale University Press. 364 pp.

SNYDER, L. H. 1954. Problems confronting human geneticists. *Am. J. Human Genet.*, 6: 108–123.

STECHER, R. M., HERSH, A. H., SOLOMON, W. M., AND WOLPAW, R. 1953. The genetics of rheumatoid arthritis. *Am. J. Human Genet.*, 5: 118–138.

STEINBERG, A. G., AND WILDER, R. M. 1952. A study of the genetics of diabetes mellitus. *Am. J. Human Genet.*, 4: 113–135.

WHITE, L. A. 1949. *The Science of Culture.* New York: Farrar, Straus, and Co., 444 pp.

Frequency and Types of Mental Retardation in Twins[1]

GORDON ALLEN AND FRANZ J. KALLMANN

Department of Medical Genetics, New York State Psychiatric Institute, New York 32, N. Y.

ALTHOUGH many specific etiologies of mental subnormality have been identified, the majority of defectives can still be classified only on a descriptive level or by elimination. This is true especially in the group of undifferentiated high-grade defectives. Even in patients of very low mentality we are not as yet consistently able to demonstrate evidence of special clinical pathology. Etiological uncertainties also remain in cases of mental defect associated with such obvious morphological or neurological abnormalities as are observed in cerebral palsy, epilepsy or mongolism. Moreover, among apparently typical "familial" cases of mental deficiency, ascribed to the multiple-factor type of inheritance, it is entirely possible that some actually are due to unrecognized unit factors or simply to some unspecified elements in an adverse environment.

In types of mental subnormality calling for exploration of the possible significance of hereditary factors, the twin-study method seems to offer the most useful initial approach. For a known clinical syndrome the method provides an estimate of the etiological importance of hereditary or germinal factors. When applied to an etiologically heterogeneous class, the method is likely to yield series both of concordant and of discordant monozygotic twin pairs, who are more revealing as probands for family investigation than any comparable sample of single-born subjects.

The medical literature abounds in reports of twins who happened to be alike or unlike with respect to some type of mental defect, but only four twin studies have been broad enough in scope and methodology to provide statistically useful information. The earliest was that of Smith (1930), who studied Danish twins. He found concordance in 11 of 13 monozygotic pairs and in only four of 50 dizygotic pairs. Rosanoff, Handy and Plesset (1937), who worked with 366 pairs of twin defectives in America, found a somewhat less striking difference between monozygotic and dizygotic twins but did not attempt to give overall concordance rates. Juda (1939, 1940) carried out an extensive twin family study in Germany based on a total of 392 twin index cases. For endogenous defect she found concordance rates of 100 per cent in monozygotic pairs and 45 per cent in dizygotic pairs. She concluded that genetic determiners of feeble-mindedness have a manifestation rate of nearly 100 per cent, and are mainly recessive. In the remaining study, Looft (1931) reported that both severe and mild retardation were frequent among twins and among the siblings of twins in Norway.

Received February 23, 1954.

[1] Presented at the annual meeting of the American Society of Human Genetics in Boston (December 27–29, 1953), as the first report on the progress of a cooperative study undertaken jointly by the Department of Medical Genetics of the New York State Psychiatric Institute and the Research Branch, National Institute of Mental Health, Public Health Service, Department of Health, Education and Welfare. G. Allen is on the staff of the National Institute of Mental Health.

The present investigation was organized with the following main objectives in view:

(1) To compare the prevalence and types of mental deficiency observed in twins with those observed in single-born individuals.

(2) To distinguish clinical syndromes among the unclassified defectives and to investigate the contributions of genetic and environmental factors in their causation.

(3) To obtain family data and twin concordance rates for all clinical entities in which such an analysis would seem likely to clarify the etiology.

The data presented in this report bear only on the first of the objectives listed.

ORGANIZATION OF THE STUDY

The twin index cases included in this study were nearly all reported as mentally defective by institutions and clinics under the supervision of the New York State Department of Mental Hygiene. The first index case falling into the collection was reported in 1937. As of December 1, 1953, the total number of subjects reported was 601, representing 478 multiple births. These include six sets of triplets and one set of quadruplets, mostly represented by a single patient. Approximately 300 of these sets are expected to be available for complete work-up, including physical examination, psychometric tests and determination of zygosity. Whenever possible, family histories and social background data are verified by home visits. The collection of historical data is extended to all index cases of potential statistical usefulness; that is, even to those pairs in which one or both partners have died.

The present report deals with statistical findings for the series of twins available at the end of November, 1953. The results of clinical, psychological and genealogical investigations will be presented in subsequent reports.

REPRESENTATIVENESS OF THE TWIN SAMPLE STUDIED

Before general conclusions can be drawn from a collection of twins, it is necessary to determine how representative they are of the population investigated. Exact information about the entire New York State population of mental defectives is not available. It is known, however, that there are about 25,000 residents in the State Schools, who probably represent between five and ten per cent of the State's total. Since 431 pairs in the present series were ascertained through these institutions, it is possible to compare the bulk of our twin sample with the institutional population from which it has been drawn.

The distribution of these 431 twin index pairs according to date of first admission is shown in table 1. The first 79 pairs represented, as completely as was practicable, the resident school population in 1937 and included one twin subject admitted as early as 1907. The remaining index cases were ascertained as new admissions, beginning with 1937. The proportion of twins ascertained among all admissions increased throughout the period 1937–1945, and since then has remained at a high level.

TABLE 1. DATE OF FIRST ADMISSION TO A STATE SCHOOL FOR 431 TWIN INDEX PAIRS

	Before 1940	1940–1944	1945–1949	1950–1953	Total
Index pairs	110	83	146	92	431
Annual rate	5.5	16.6	29.2	23.0	12.6

TABLE 2. ASCERTAINED TWIN RATES FOR FIVE NEW YORK STATE SCHOOLS (1948–1951)

	Letch-worth Village	Newark	Syracuse	Wassaic	Willow-brook	Total
Patients admitted	1299	803	511	1024	1082	4719
Twin index cases	47	16	20	31	33	147
Twin index pairs (represented by one or both partners)	40	15	13	24	30	122
Twin index cases per 100 patients	3.6	2.0	3.9	3.0	3.0	3.1
Pairs represented per 100 patients	3.1	1.9	2.5	2.3	2.8	2.6

In a representative sample of twins from the State of New York, one-third are expected to come from opposite-sex pairs, one-third from same-sex dizygotic pairs, and one-third from monozygotic pairs (Yerushalmy and Sheerar, 1940). In the present series there are 558 index cases whose partners are of known sex. Of these, 175 have opposite-sex partners and 383 have same-sex partners, corresponding to 31.4 per cent and 68.6 per cent, respectively. This is not a significant deviation from the expected one-third and two-thirds. However, if we make the usual assumption (Weinberg, 1901) that the number of same-sex dizygotic pairs is equal to the number of opposite-sex pairs, then 383 less 175, or 208, are monozygotic. Since in the usual sample there would be one-third, or 186 monozygotic twins, the present series appears to contain an excess of 22 monozygotic index cases. This difference would be significant at the five-per-cent level if it were confirmed in the final zygosity classification.

One way to assess the completeness of ascertainment in the present sample would be to compare the number of twins observed with the number of twins expected. In the State of New York, the frequency of twins at birth is 1.1 pairs per 100 deliveries (Yerushalmy and Sheerar, 1940). If this rate is corrected for stillbirths and neonatal deaths (Karn, 1953), it corresponds to about two twin individuals per 100 persons of the New York population. Table 2 shows the twin rate, excluding triplets and quadruplets, for those years and schools in which ascertainment seems to have been nearly perfect, and for which general admission data are available. The average twin rate, 3.1 index cases per 100 admissions, is much higher than the expected two per cent. This excess remains significant at the .01 level of probability even after all cases of cerebral palsy and birth trauma, possible consequences of twinning, have been discounted. The differences among the schools are not statistically significant.

In one section of Norway, Looft found two per cent of twins among registered defectives with I.Q. below 70, but the figure was 3.6 per cent in a group of retarded (borderline) school children. Rosanoff and Inman-Kane (1934) found more twins among institutionalized mental defectives than in other institutional populations. The latter authors ascribed both sets of observations to the fact that twins have relatively unfavorable conditions of gestation and birth.

The data presented in tables 3, 4, and 5 show that birth factors may not fully explain the high frequency of twins observed in institutions. It is true that post-traumatic and cerebral palsy cases are relatively more frequent among the twin defectives (table 3) and especially among those whose partners died in infancy (table 4). However, the numbers in these two groups are not large enough to explain the total excess of defective twins observed. In table 5 one sees at once that the frequen-

TABLE 3. ADMISSION DIAGNOSES OF TWINS COMPARED WITH SINGLE-BORN (STATE SCHOOLS 1935–1950)

Diagnostic Group	Single-born		Twin Cases		x^2
	Number	Per cent	Number	Per cent	
Undifferentiated	9409	41.6	137	34.8	4.3
Familial	6991	30.9	139	35.3	2.3
Mongolism	1406	6.2	22	5.6	0.2
Cranial anomaly	686	3.0	18	4.6	2.8
Cerebral palsy	704	3.1	23	5.8	8.8
Post-infectional	910	4.0	4	1.0	8.9
Post-traumatic	997	4.4	32	8.1	11.8
Miscellaneous	1527	6.7	19	4.8	2.1
Total	22630	99.9	394	100.0	41.2

TABLE 4. INSTITUTIONAL DIAGNOSES OF TWINS WHOSE PARTNERS WERE STILL-BORN OR DIED IN INFANCY (STATE SCHOOLS 1935–1950)

Diagnostic Group	Number	Per Cent
Undifferentiated	14	33.3
Familial	10	23.8
Mongolism	1	2.4
Cranial anomaly	2	4.8
Cerebral palsy	5	11.9
Post-infectional	0	0.0
Post-traumatic	6	14.3
Miscellaneous	4	9.5
Total	42	100.0

TABLE 5. TWIN RATES BY DIAGNOSIS FOR THE SAME SCHOOLS AND YEARS AS IN TABLE 2

Diagnostic Group	All Admissions	Twin Index Cases	Twin Cases per 100 Admissions
Undifferentiated	1954	45	2.3
Familial	1002	41	4.1
Mongolism	462	11	2.4
Cranial anomaly	332	7	2.1
Cerebral palsy	227	6	2.6
Post-infectional	163	3	1.8
Post-traumatic	307	19	6.2
Miscellaneous	272	15	5.5
Total	4719	147	3.1

cies are above the expected level of two per cent in most groups, including mongolism. The only exception is the post-infectional group, where the observed frequency falls below expectation.

Evidently, a comparison of single-born and twin defectives reveals a relative excess of twin cases caused apparently by gestational and natal influences, chiefly in the

post-traumatic and cerebral palsy groups. It also appears that mentally defective twins of all types are more likely to enter the N. Y. State Schools than are single-born defectives of the same types. However, the annual admission rate for twins may vary excessively; disproportionately large numbers of twins were admitted in 1948 and 1949. Until more extensive data are available, the significance of the high overall twin rate cannot be assessed.

AGE AND SEX OF THE SAMPLE

The median year of birth for the entire sample of twins is 1934, making the median age 20 years. Actually, some of the older index cases are dead, while others have been discharged and can no longer be located. Therefore, the age of the cases available for analysis is expected to be lower. For 65 pairs studied so far, the median age was 14 years.

The overall sex ratio in the present series of index cases is 107.2 males to 100 females. An excess of males, which according to Malzberg (1953) is expected in most categories of mental defect, is found in this sample only in the undifferentiated, familial, and mongoloid groups. The respective figures for males are 129, 129 and 154. In most of the other categories, there is an unaccountable excess of females.

CONCORDANCE RATES

Certain facts with respect to concordance are striking when mentally defective twins are ascertained through public institutions. Many pairs entered this survey as concordant at the time of the initial report, simply because they had been institutionalized together. In fact, it appears that the majority of the concordant cases can be readily detected in this manner. An exact classification of all twins is not yet possible, either by diagnosis or by zygosity, but even at this stage the material affords some indication of a gene-controlled etiology in many cases of mental deficiency.

Intra-pair differences in sex permit a preliminary sorting of the pairs by zygosity, although only about one-half of the same-sex pairs are monozygotic. The results of such a crude analysis are presented in table 6 for those index pairs in whom the co-twin survived infancy and was of known sex. The high proportion of concordant pairs

TABLE 6. PROPORTIONS OF SAME-SEX AND OPPOSITE-SEX PAIRS REPRESENTED BY TWO INDEX CASES

Diagnostic Group	Same-sex Pairs		Opposite-sex Pairs	
	Total	Pairs with 2 index cases	Total	Pairs with 2 index cases
Undifferentiated	77	36	43	2
Familial	75	51	41	15
Mongolism	8	3	12	0
Cranial anomaly	11	2	7	0
Cerebral palsy	8	2½*	7	0
Post-traumatic	13	0	13	0
Other diagnoses	9	1½*	8	0
Total	201	96	131	17

* One patient each, with cerebral palsy and glandular disorder, had an "undifferentiated" twin partner.

in table 6 as compared with table 2 is accounted for by the last two restrictions, together with some apparent preferential ascertainment of concordant pairs in the early years of collection.

In the same-sex group it is significant that pairs with two institutionalized partners occur in every major category of mental deficiency. In the opposite-sex group, institutionalization of both twins is observed only among the undifferentiated and familial types, and much less frequently than in same-sex pairs. This difference is highly suggestive of the operation of genetic factors, but it may not be entirely due to increased concordance in monozygotic twins. According to Rosanoff, Handy and Plesset (1937), dizygotic twins of the same sex also have a higher concordance rate than opposite-sex pairs.

SUMMARY

This is a preliminary report on a study of mentally retarded twins and deals largely with general statistical data. At the time of analysis, the series included 601 index cases representing 478 multiple births. The earliest admission was in the year 1907, and ascertainment is almost complete for recent admission years (1945 and thereafter).

In the institutional population studied, twins were found to constitute 3.1 per cent of all admissions, as compared with about two per cent of twins expected in the general population of the State of New York. The observed excess of twins occurs in all major diagnostic categories and seems to be only partly explained by factors related to twinning per se.

In every major diagnostic category listed, concordance with respect to certified mental deficiency is more frequent in same-sex than in opposite-sex twin pairs. For some categories concordance is found only in same-sex pairs. More detailed studies are in progress.

REFERENCES

Juda, A. 1939, 1940. Neue Psychiatrisch-Genealogische Untersuchungen an Hilfsschulzwillingen und ihren Familien. *Zschr. Neur.*, 166: 365–452; 168:448–491; 168: 804–826.

Karn, M. N. 1953. Data of twin births occurring in 2 English metropolitan hospitals. *Acta genet. med. gemellol.*, 2: 152–163.

Looft, C. 1931. L'évolution de l'intelligence des jumeaux. *Acta paediatrica*, 12: 41–74.

Malzberg, B. 1953. Sex differences in the prevalence of mental deficiency. *Am. J. Ment. Def.*, 58: 301–305.

Rosanoff, A. J., and Inman-Kane, C. V. 1934. Relation of premature birth and under-weight condition at birth to mental deficiency. *Am. J. Psychiat.*, 90: 829–852.

Rosanoff, A. J., Handy, L. M., and Plesset, I. R. 1937. The etiology of mental deficiency with special reference to its occurrence in twins. *Psychol. Monographs*, Vol. 48, No. 216.

Smith, J. C. 1930. Das Ursachenverhältnis des Schwachsinns beleuchtet durch Untersuchungen von Zwillingen. *Zschr. Neur.*, 125: 678–692.

Weinberg, W. 1901. Beiträge zur Physiologie und Pathologie der Mehrlingsgeburten beim Menschen. *Arch. f. ges. Physiol.*, 88: 346–430.

Yerushalmy, J., and Sheerar, S. E. 1940. Studies on twins. I. The relation of order of birth and age of parents to the frequency of like-sexed and unlike-sexed twin deliveries. *Human Biology*, 12: 95–113.

Two Different Mutations of the X-Chromosome Causing Diabetes Insipidus

HANS FORSSMAN

Psychiatric Clinic, University of Gothenburg, Sweden

LACOMBE (1841) was the first to draw attention to the familial occurrence of diabetes insipidus, describing a family with eight affected members. Since his report there have been at least fifty others on the hereditary occurrence of this disorder. As has often happened in the history of human genetics, the families in which there were many affected persons were the first to attract attention and gain publicity. Two large families have now become classical in the literature on diabetes insipidus, the one described by Adolph Weil (1884) and Alfred Weil (1908), Camerer (1935) and Dölle (1951) and the one reported by Lauritzen (1893) and Ellermann (1939). These two families have given rise to the widespread belief that inherited diabetes insipidus is always due to the operation of a dominant autosomal gene. The result is that it has been difficult to accept the idea that the disorder may be transmitted by other kinds of genes.

In 1888 the possibility of diabetes insipidus being derived from an X-linked gene was suggested but rejected by Liebmann. The question was brought up again by Weil (1908), Jansen and Broekman (1921), Weitz (1936) and Hanhart (1940), but none of these authors could produce what they felt to be convincing proof of this form of inheritance. McIlraith (1892) and Komai (1934) described families which we should now consider to exhibit sex-linked diabetes insipidus. Furthermore, a number of small families have been reported which might well be examples of this manner of inheritance, but with too few affected persons to permit any definite conclusions.

In 1945 I published the result of a search for families with diabetes insipidus in Sweden. In addition to two families in which the disorder was due to autosomal genes, I was able to present three family trees, one very large, which showed that the condition could also be sex-linked. As a matter of fact, this proved to be by far the most common manner of inheritance in Sweden. Through my genealogic research I was able to connect up persons with diabetes insipidus with likewise afflicted relatives of whose existence they were unaware. This illustrates what is obvious—that many of the sporadic cases are genetically determined.

Two years later Williams and Henry (1947) reported a family with X-linked diabetes insipidus. The existence of X-linked forms of this disorder was afterward accepted by several different authors (Smith 1951, Pender and Fraser 1953, Sorsby 1953 and others), but many still recognize only the autosomally determined type (Ford 1948, Blothner 1953).

Sex-linked diabetes insipidus can be caused by two different genes, one of which produces a form showing ordinary susceptibility to the antidiuretic hormone and the other a form characterized by complete lack of response (Forssman 1945, Williams

Received June 11, 1954.

and Henry 1947). In his textbook of 1950 Wilkins mentioned the pitressin-refractory sex-linked form, which Williams and Henry called "nephrogenic", but not the more common sex-linked form characterized by ordinary susceptibility to the antidiuretic hormone.

Since 1945 my material has been increased. The chances of a scientific report being read decrease with size, but the reverse is true of pedigrees. In 1945 the pedigree of my large family was printed in seven separate sections. Here it is shown in its present enlarged form as a whole (fig. 1). Undisputable proof of X-linked heredity is only present in the parts of the pedigree which are given in detail, i.e., where the symbols for the afflicted members are entirely filled in with black. The prolongation of the pedigree backward to a common ancestor, a woman born in 1712, is only one of several possibilities. However, the depicted genetical route is not chosen at random, for it is one which does not include any passage from father to son and is therefore

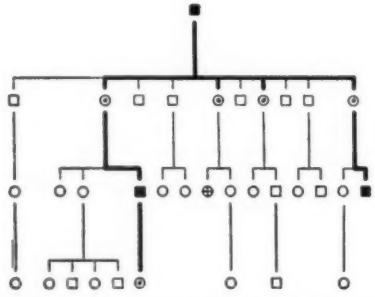


FIG. 2. Another pedigree showing recessive inheritance of diabetes insipidus of pituitrin-susceptible type. The symbols are explained on page 25.

compatible with an X-linked pattern. The character in question being so rare, there is a good chance that the gene followed the course depicted here. The members of this pedigree showed ordinary susceptibility to the antidiuretic hormone.

Figure 2 is a family tree showing the same clinical type of diabetes insipidus as the one in figure 1. The three afflicted members lived in the same parish as some of the members of the first pedigree. Consequently there is reason to suspect that figure 2 is actually a fragment of figure 1. However, I have not been able to find enough data to join the two.

I personally examined 16 of the 26 unequivocally afflicted males from these two families. Another case was clinically verified elsewhere. The diagnosis in the other 9 cases is based on information received from close relatives. Several of these nine were dead at the start of my investigation. I tested the effect of the antidiuretic hormone in 11 of the 26 men and all eleven reacted in a typical manner to the hormone.

Some of the female heterozygotes were entirely free from symptoms and others exhibited slight traces of the disorder, sometimes only demonstrable as lack of ability to concentrate urine on being deprived of fluid. An interesting feature is that several

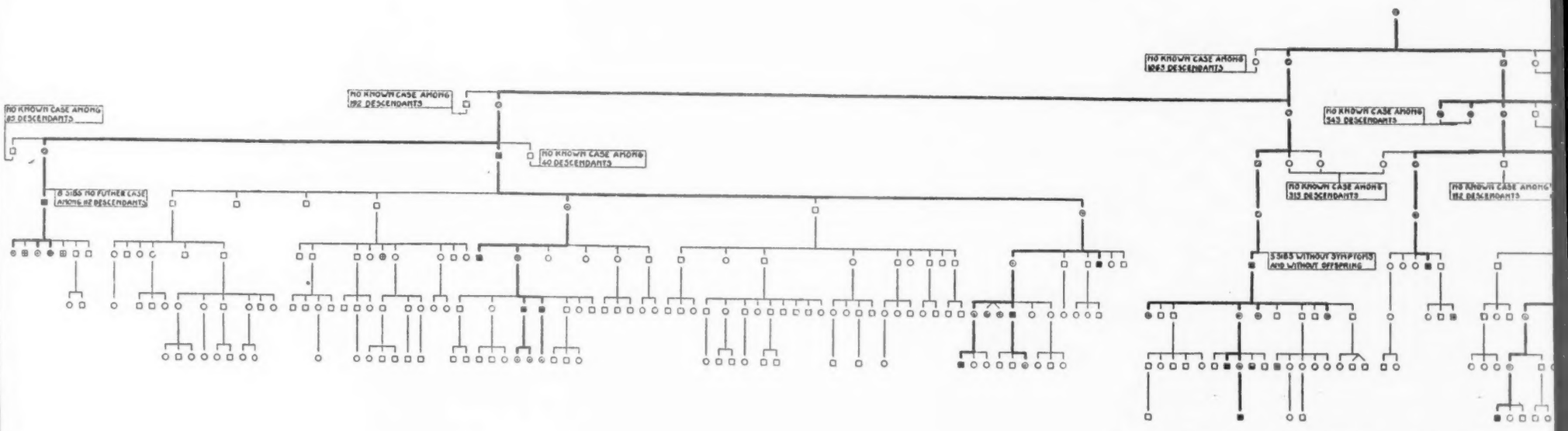

NO KNOWN CASE AMONG 89 DESCENDANTS
NO KNOWN CASE AMONG 192 DESCENDANTS
NO KNOWN CASE AMONG 40 DESCENDANTS
NO KNOWN CASE AMONG 1063 DESCENDANTS
NO KNOWN CASE AMONG 343 DESCENDANTS
NO KNOWN CASE AMONG 315 DESCENDANTS
5 SIBS WITHOUT SYMPTOMS AND WITHOUT OFFSPRING

FIG. 1. Pedigree showing sex-linked recessive inheritance of diab

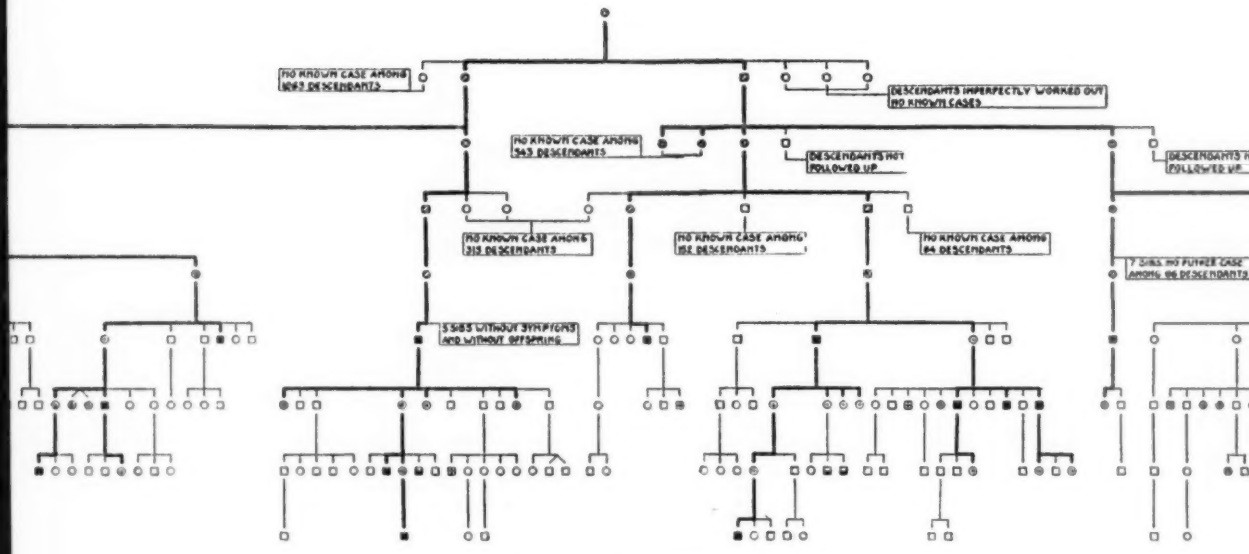
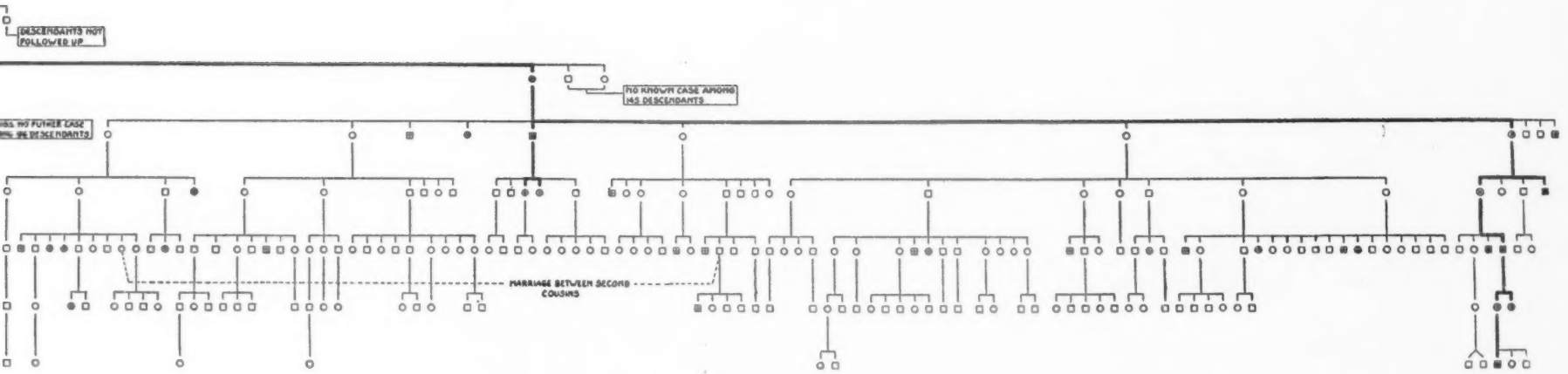


FIG. 1. Pedigree showing sex-linked recessive inheritance of diabetes insipidus of pituitrinsusceptible type. The symb



e. The symbols are explained on page 25.

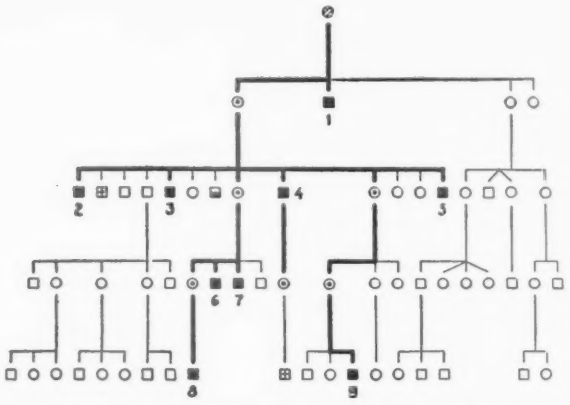


FIG. 3. Pedigree showing sex-linked recessive inheritance of diabetes insipidus of so-called nephrogenic type, refractory to pituitrin. The symbols are explained on page 25.

of the conductors suffered from a full-blown diabetes insipidus syndrome the last four months of pregnancy, and became free of the disorder a few days after delivery.

Figure 3 depicts my third family. The sex-linked manner of inheritance is likewise obvious there. In 6 of the 9 cases the presence of the disorder was confirmed clinically. Case 1, dating a hundred years back, is documented by entries in the 1897 hospital record of number 3. In the two remaining cases, the disorder is documented by evidence from close relatives.

I was able to test the effect of the antidiuretic hormone in four of the cases, numbers 4, 7, 8 and 9. Three of the patients were tested on several occasions and with different preparations. They all proved to be totally unresponsive to the hormone. Figure 4 compares the reaction of a responsive patient from the pedigree in figure 1 with that of an unresponsive patient from the pedigree in figure 3. The curves represent the chloride concentration and specific gravity of the urine at half-hourly intervals on two days, on the second of which an injection of pituitrin was given at the start. The patients, 19 and 23 years old, were tested with ampuls from the same package, manufactured in the same batch. There is obviously an absolute difference in the pathogenic mechanism of the cases from figure 3 and the cases from the first two families. The syndrome seems to take an unusually severe form in cases of the unresponsive type.

Many authors have observed that hereditary diabetes insipidus is more common in males than in females (Weil 1908, Jansen and Broekman 1921, Chester and Spiegel 1933, de Lange 1935, Warkany and Mitchell 1939, Scherrer 1940, Hanhart 1940, Wilkins 1950), and this has perplexed the ones who only accept the autosomal manner of inheritance. In 1940 Hanhart tabulated 25 pedigrees, containing 169 affected subjects of whom 108, or 63.9 per cent, were males. There is a significant difference between this figure and the 50 ± 3.85 to be expected on random distribution of the sexes. Today, if I were to add all the cases reported together with a number of my

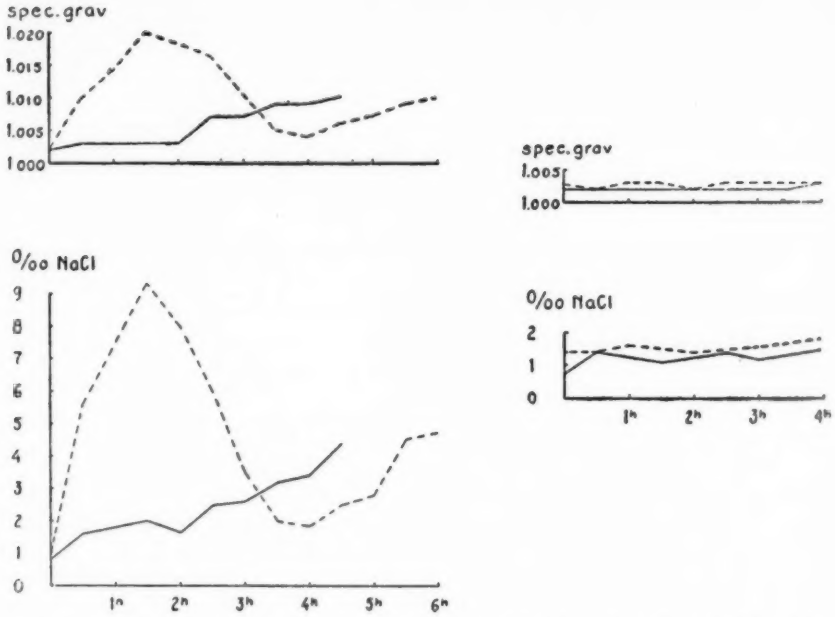


FIG. 4. Comparison between reaction to pituitrin of a subject from the pedigree in figure 1 (on the left) and of a subject from the pedigree in figure 3 (on the right). The curves show the chloride concentration and specific gravity of urinary samples taken at half-hour intervals on two different days, one when pituitrin was given at the start (broken lines) and one when no pituitrin was given (unbroken lines). The subjects were of practically the same age and the ampuls of pituitrin came from the same package.

yet unpublished ones, I should get a sum of 382 of which 244, or again 63.9 per cent, are males. The difference between this figure and the expected 50 ± 2.56 per cent is more than five times the standard error.

It now being known that there are X-linked genes for diabetes insipidus, there is no longer any point in calculating the sex ratio in material that is not genetically homogeneous. In order to determine the sex ratio in a material free of the sex-linked form, I collected the cases from the families in the literature in which there was undisputable evidence of a father-to-son passage. The reports of Chase (1927) and Bonnet (1936) do not give complete evidence regarding the sex of the affected subjects and so could not be included. These cases, collected in table 1, include 140 males and 96 females. However, as the father-to-son passage requires at least two males, the figure 140 must be reduced by two men for each of the families in question. There being eighteen families, this makes 104 males to 96 females. The percentage of males then becomes 52, a figure which deviates less than the amount of the standard error from the expected 50 ± 3.54 per cent. Accordingly, the higher liability of males

TABLE 1. SEX DISTRIBUTION IN PUBLISHED CASES OF DIABETES INSIPIDUS FROM FAMILIES SHOWING FATHER-TO-SON PASSAGE

Authors	Publ. Year	Males	Females
Lacombe	1841	5	3
Pain	1879	5	2
Knöpfelmacher	1905	3	2
Jansen and Broekman	1921	4	10
Martinez and Navarro	1922	7	1
Gänsslen and Fritz	1924	10	9
Peterman	1929	3	0
Levit and Pessikova, fam. b)	1936	3	0
Ellermann (including Lauritzen 1893)	1939	15	11
Steiner, fam. b)	1939	3	6
Scherrer	1940	2	1
Thaddea and Kleinschmidt	1942	7	4
Harding	1943	2	3
Fontan, Verger, Bontégeat and Mouliès	1944	7	3
Forssman, fam. K	1945	3	3
Weller, Elliott and Gusman	1950	14	4
Dölle (incl. Weil 1884, Weil 1908 and Camerer 1935)	1951	26	18
Pender and Fraser	1953	21	16
Total		140	96

to the disorder which so many authors have noted is fully explained by the existence of X-linked genes. In other words, the X-linked genes are probably not so rare as formerly believed.

Most likely there will prove to be a number of instances of X-linked inheritance in various countries, once geneticists and physicians become aware of the possibility. Every new X-linked gene is of special interest to the work on the map of the X-chromosome.

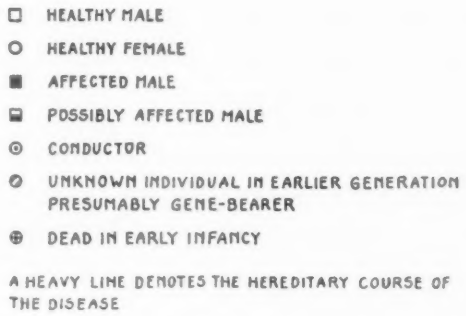


FIG. "A"

SUMMARY

The paper reports three Swedish families in which diabetes insipidus was inherited as a sex-linked recessive, though the heterozygotic females sometimes showed slight signs or symptoms of the disorder. The smallest pedigree is probably a fragment of the largest one. The afflicted members of these two families responded in a typical way to the antidiuretic hormone. The four examined members of the third family, on the other hand, proved to be totally insensitive to the hormone, exhibiting so-called nephrogenic diabetes insipidus. Accordingly, diabetes insipidus can be derived not only from autosomal genes but also from two different types of sex-linked genes.

The author calculated the sex ratio in the cases from the families in the literature in which a father-to-son passage occurred, and found the ratio of 1 to 1 to be expected in the case of autosomal genes. Inasmuch as the literature contains a preponderance of male cases, the author concluded that sex-linked diabetes insipidus is not so rare as commonly supposed.

REFERENCES

BLOTNER, H. 1951. Diabetes Insipidus, New York, Oxford University Press.

BONNET, R. 1936. Contribution à l'étude du diabète insipide, Thesis, Lyon.

CAMERER, J. W. 1935. Eine Ergänzung des Weilschen Diabetes-insipidus-Stammbaumes, *Arch. Rassenb.* 28: 382.

CHASE, L. 1927. Hereditary diabetes insipidus, *Canad. M. Ass. J.* 56: 212.

CHESTER, W. AND SPIEGEL, L. 1933. Hereditary diabetes insipidus, *J. Am. M. Ass.* 100: 806.

DÖLLE, W. 1951. Eine weitere Ergänzung des Weilschen Diabetes-insipidus-Stammbaumes, *Ztschr. menschl. Vererb.* 30: 372.

ELLERMANN, M. 1939. Le diabète insipide héréditaire, *Acta psychiat. neur. Kbn.* 14: 233.

FONTAN, VERGER, BENTÉGEAT AND MOULIÈS. 1944. Le diabète insipide héréditaire et familial, *J. méd. Bordeaux* 121: 161.

FORD, E. B. 1948. Genetics for Medical Students, ed. 3, London, Methuen & Co., Ltd.

FORSSMAN, H. 1945. On hereditary diabetes insipidus, *Acta med. Scand.* supp. 159, (which contains an extensive list of references).

GÄNSSLEN, M. AND FRITZ. 1924. Ueber Diabetes insipidus, *Klin. Wschr.* 3: 22.

HANHART, E. 1940. Die Erbpathologie des Diabetes insipidus, in Handbuch der Erbbiologie des Menschen, Berlin, vol. IV: 2 p. 798.

HARDING, F. E. 1943. The pituitary antidiuretic hormone in diabetes insipidus, *West. J. Surg.* 51: 269.

JANSEN, E. AND BROEKMAN, J. 1921. Een Geval van hered. Diabetes insipitus, *Nederl. tschr. geneesk.* Series 2, 65: 2519.

KNÖPFELMACHER, W. 1905. Diabetes insipidus bei Kindern, *Münch. med. Wschr.* 52: 629.

KOMAI, T. 1934. Cited by Hanhart 1940.

LACOMBE, L. U. 1841. De la polydipsie, *J. méd. chir.* 7: 305, 323, 339.

DE LANGE, C. 1935. Ueber erblichen Diabetes insipidus, *Jahrb. Kinderh.* Series 3, 145: 1.

LAURITZEN, M. 1893. Om hereditaer diabetes insipidus, *Hospitalstidende* Series IV: 1 & 2, 352, 392, 423, 451.

LEVIT, S. G. AND PESSIKOVA, L. N. 1936. The genetics of diabetes insipidus. *J. Hered.* 27: 445.

LIEBMANN, A. 1888. Ueber Diabetes insipidus bei Kindern, Thesis, Berlin.

MARTINEZ, G. N. AND NAVARRO, A. 1922: Zwei Fälle der familiären Form des idiopathischen Diabetes insipidus mit Hypophysenbehandlung, Rev. circ. méd. Córdoba, 10: 78, abstracted *Zbl. inn. Med. Grenzgeb.* 26: 363, 1923.

MCILRAITH, C. H. 1892. Notes on some cases of diabetes insipidus, *Lancet* 2: 767.

PAIN, G. 1879. Notes à propos de quelques observations de polyurie chronique, Thesis, Paris.

PENDER, C. B. AND FRASER, F. C. 1953. Dominant inheritance of diabetes insipidus. *Pediat.* 11: 246.

PETERMAN, M. G. 1929. Diabetes insipidus, *Am. J. Dis. Child.* 38: 1335.
SCHERRER, J. 1940. Ueber den Diabetes insipidus und seine vererbbare Form, Thesis, Zürich.
SMITH, H. W. 1951. The Kidney, New York. Oxford University Press.
SORSBY, A., ed. 1953. Clinical Genetics, London, Butterworth & Co., Ltd.
STEINER, F. 1939. Zur Erblichkeit des Diabetes insipidus, *Erbarzt* 7: 89.
THADDEA, S. AND KLEINSCHMIDT, A. 1942. Zur Kenntnis der familiären hereditären Form des Diabetes insipidus, *Endokrinologie* 25: 57.
WARKANY, J. AND MITCHELL, A. G. 1939. Diabetes insipidus in children, *Am. J. Dis. Child.* 57: 603.
WELLER, C. G., ELLIOTT, W. AND RODRIGUEZ GUSMAN, A. 1950. Hereditary diabetes insipidus, *J. Urol.* 64: 716.
WEIL, ADOLPH. 1884. Ueber die hereditäre Form des Diabetes insipidus. *Arch. path. Anat.* 95: 70.
WEIL, ALFRED. 1908. Ueber die hereditäre Form des Diabetes insipidus, *Deutsches Arch. klin. Med.* 93: 180.
WEITZ, W. 1936. Die Vererbung innerer Krankheiten, Stuttgardt, Ferdinand Enke.
WILKINS, L. 1950. The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., Charles C Thomas, p. 293.
WILLIAMS, R. H. AND HENRY, C. 1947. Nephrogenic diabetes insipidus, *Ann. Int. M.* 27: 84.

A Pedigree of Aniridia with a Discussion of Germinal Mosaicism in Man[1]

T. EDWARD REED AND HAROLD F. FALLS

Heredity Clinic, Institute of Human Biology and Department of Ophthalmology, University Hospital, University of Michigan, Ann Arbor

INTRODUCTION

CONGENITAL aniridia is an abnormality of interest to both the ophthalmologist and the human geneticist. This defect, occurring in about one person in 100,000 (Møllenbach, 1947), concerns the former because of the severe visual handicap it produces and because of the questions about embryology of the iris it raises. The latter is interested because it is inherited as if due to a dominant gene of high penetrance and so may be studied with regard to its formal genetics, mutation rate, selective value, and linkage with other genes.

In a strict sense "aniridia" is not a precise term since some iris is always present microscopically, and because the iris may be affected in several different ways. The anterior layer of the iris, the stroma, is of mesodermal origin and appears first; the posterior layer, which is an extension of the optic cup and hence of neuro-ectodermal origin, appears after the mesodermal layer is in place. Aniridia may involve the absence of the stroma only, the absence of the posterior layer only, or both. In addition to the absence of some of the elements of the iris, congenital aniridia is usually characterized by aplasia of the macula, nystagmus, and photophobia. In early childhood, and perhaps until middle age, an aniridic person may have fair visual acuity, but in later life blindness often sets in as a result of secondary changes in the eye. Although unilateral aniridia is known, the amount of iris present tends to be equal in the two eyes of an individual, and is fairly constant in affected members of a given family. Not infrequently, however, considerable variation is found, ranging from nearly complete absence of the iris to a very mild coloboma.

Aniridia is characteristically inherited as if due to a simple autosomal dominant gene (Bell, 1932; Waardenburg, 1932; Møllenbach, 1947; Sorsby, 1951). Other modes of inheritance have been reported (Sorsby, 1951) but appear to be uncommon. The penetrance of the gene is high but perhaps not unity. Cases are known in which a person having an aniridic parent and an aniridic child has only a slight coloboma, and less authenticated cases are reported in which such persons are reported to be normal. An estimate of the penetrance will be given later in this paper. Two linkage studies have been made (Beattie, 1947; Mohr, 1953); no linkage was found between the locus of the gene for aniridia and the loci for the ABO, MN, Rh, P, Lewis, Lutheran, and Duffy blood groups or with the locus for taste sensitivity to phenylthiocarbamide. The first occurrence of aniridia in a family is believed by Møllenbach

Received October 13, 1954.

[1] This study was supported in part by the Bishop Fund of the Institute of Human Biology, University of Michigan.

(1947) to be caused by mutation of the normal allele to the aniridia-producing allele and has been estimated by him to occur with a frequency of 0.5×10^{-5} mutations/gene/generation. From Møllenbach's data, showing 22 of 44 cases to be mutants, it is estimated (Haldane, 1949) that the relative fertility of persons with aniridia is about 0.5. However, Beattie (1947) found no reduction of fertility in his single large kindred. It may be noted that these estimates of frequency, mutation rate, and fertility derived from Møllenbach's data are not mutually consistent for a population in equilibrium.

MATERIAL AND METHODS

This paper reports on studies made on a kindred living in the Lower Peninsula of Michigan and consisting of 99 apparently normal and 23 aniridic individuals. Thirty-eight of the normal persons and 20 of the aniridic persons were examined ophthalmologically and blood typing was done on samples from 27 persons whose blood types could give information as to the existence of linkage between the locus of the

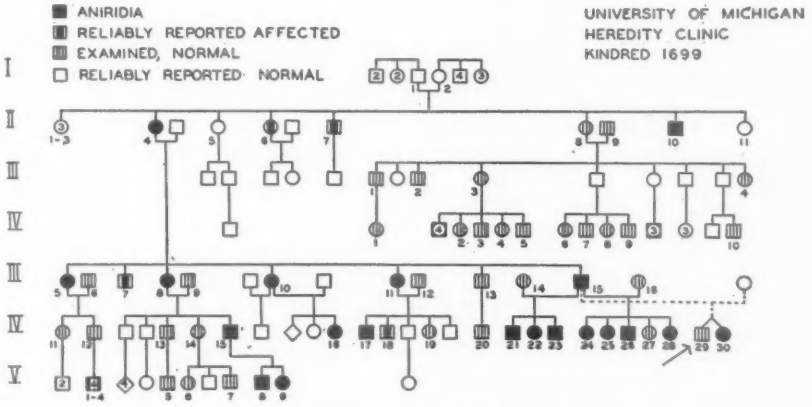


FIG. 1. Pedigree of the kindred studied

gene for aniridia and the loci of the genes for the ABO, Rh, and MN blood groups. The members of the kindred are of Caucasian ancestry and, among the living, range in age from two months to 73 years, distributed in four generations. A pedigree of the kindred is shown in Figure 1. The propositus through whom the kindred came to be studied is IV-29, a normal, five-year-old illegitimate boy who is a twin of an aniridic girl. He was referred to the Heredity Clinic for an appraisal of the possible effect on his adoption of having aniridic relatives. The information obtained on the condition of the eyes of persons who could not be examined is believed to be quite reliable, at least as regards the presence or absence of aniridia, since whenever descriptions were later checked they were found to be correct.

RESULTS

The results of the ophthalmological examinations and blood grouping are given in Table 1.

TABLE 1. DESCRIPTIONS AND EXAMINATION RESULTS

Individual	Sex	Age if Living	Age at Death	Ophthalmologically Examined	Aniridic	Blood Groups
I- 1	M		65	−	−*	
2	F		84	−	−*	
II- 1, 2, 3	F		<6	−	−	
4	F	73		+	+	O; N; R_1R_1
5	F		24	−	−	
6	F		32	−	+	
7	M		64	−	+	
8	F	64		+	−	O; N; R_1R_1
9	M	77		+	−	
10	M	62		+	+	O; MN; R_1R_1
11	F		1	−	−	
III- 1	M	44		+	−	
2	M	39		+	−	
3	F	36		+	−	
4	F	18		+	−	
5	F	55		+	+	O; N; R_1R_2
6	M	65		+	−	O; MN; R_1r
7	M		23	−	+	
8	F	50		+	+	O; MN; R_1R_1
9	M	63		+	−	A; M; R_1r
10	F	45		+	+	
11	F	44		+	+	O; MN; R_1R_2
12	M	53		+	−	AB; MN; R_1R_1
13	M	42		+	−	O; MN; R_1R_2
14	F	32		+	−	A; N; R_1r
15	M	38		+	+	O; MN; R_1R_2
16	F	28		+	−	O; N; R_1R_1
IV- 1	F	10		+	−	
2	F	9		+	−	
3	M	7		+	−	
4	F	6		+	−	
5	M	4		+	−	
6	F	12		+	−	
7	M	11		+	−	
8	F	10		+	−	
9	M	9		+	−	
10	M	3		+	−	
11	F	36		+	−	O; MN; R_2r
12	M	34		+	−	O; MN; R_1R_1
13	M	28		+	−	O; MN; R_1R_1
14	F	27		+	−	O; MN; R_1r
15	M	23		+	+	
16	F	8		+	+	
17	M	26		+	+	B; M; R_1R_2
18	M	25		−	+	
19	F	13		+	−	A; MN; R_1R_2
20	M	16		+	−	
21	M	16		+	+	O; MN; R_2r
22	F	14		+	+	O; N; R_1r
23	M	12		+	+	A; N; R_2r
24	F	8		+	+	O; MN; R_1R_1

TABLE 1—*Continued*

Individual	Sex	Age if Living	Age at Death	Ophthalmologically Examined	Aniridic	Blood Groups
25	F	7		+	+	O; N; R_1R_2
26	M	5		+	?†	O; MN; R_1R_2
27	F	3		+	−	O; MN; R_1R_2
28	F	2		+	+	O; MN; R_1R_1
29	M	4		+	−	
30	F	4		+	+	
V- 1	F	11		+	−	
2	F	10		+	−	
3	F	8		+	−	
4	M	6		+	−	
5	M	4		+	−	
6	F	4		+	−	
7	M	½		+	−	
8	M	3		+	+	
9	F	4		+	+	

* Considered non-aniridic on basis of report by a reliable, normal daughter and inspection of photographs taken at age 28 and 22. I-1, however, appeared to have a slightly elliptical, centrally positioned, right pupil. Since the photograph is a somewhat fuzzy enlargement it is not known whether this defect is real or not. No ocular abnormality or visual dysfunction was known to the normal daughter.

† Brown iris was present but in both eyes there was hypoplasia of the iris stroma, ectopia pupillae (displaced up and in), dyscoria, nystagmus, alternating convergent strabismus, photophobia, and narrowed palpebral fissures. Vision in each eye was 6/30 −1.

The pedigree data have been examined for possible aberrant segregation ratios of aniridic to normal among the children of aniridic parents. Using data from the eight matings in which most or all of the children were examined, and making all possible comparisons with respect to sex and presence or absence of aniridia, no significant departures from equality of the numbers of affected and non-affected and numbers of males and females were found. Individual IV-30 was omitted from the count when determining segregation ratios, and her affected father, III-15, who served to call attention to his sibship, was likewise omitted from the segregation count. Three aniridic persons, II-6, II-7, and III-10, had children of whom most or all were not examined. When their children are added to those of the previous eight matings there are still no significant departures from equality. The data are consistent with the interpretation of simple dominant inheritance of aniridia, although, as is evident from Table 1, especially in the description of IV-26, the expression of the condition in various persons may vary widely.

The possibility of genetic linkage between the locus of the gene for aniridia and the loci of the ABO, MN, and Rh blood groups was investigated. The data provide no information with regard to the ABO system since all aniridic parents have O blood. Four useful matings were available for the MN and Rh systems and, using the method of Finney (1940, 1942), λ and κ_c scores were calculated, being −2 and 14 respectively for MN and −5 and 15 for Rh. Thus there is no suggestion of linkage. One study of

linkage with aniridia, that of Beattie (1947), made use of the ABO, MN, Rh, and P blood groups as well as taste response to phenylthiocarbamide. Slight evidence for linkage with the locus for the ABO system was found and the matter was thought worth further investigation. Another linkage study, that of Mohr (1953) made use of these markers and also the Lewis, Lutheran, and Duffy blood groups. No evidence for linkage was found.

There are too few individuals for a reliable calculation of the relative fertility, but it is clear that, in this kindred, persons with aniridia suffered little loss of fertility.

DISCUSSION

The gene producing aniridia in this kindred has been found to segregate in the normal manner, showing simple autosomal dominance and high penetrance, and cannot be shown to be linked with the genes for the ABO, MN, and Rh blood group systems. These facts require no comment but the question of the origin of the gene, which apparently first became evident in four aniridic sibs in Generation II, raises some fundamental questions. (The probability of four separate mutations would appear to be so small that this possibility will be disregarded.) The explanation for this multiple appearance of affected sibs therefore seems to lie in one of two possibilities: either a parent, I-1 or I-2, had the gene for aniridia and did not show it, or a mutation at the aniridia locus from normal to aniridic occurred early in the development of a parental gonad, so that an appreciable portion of the gonad became heterozygous for the aniridia-producing allele, making a so-called germinal or gonadic mosaic. Since the gene for aniridia is believed to have high penetrance, and since there are at least six demonstrated cases of germinal mosaicism (GM) in experimental mammals, the choice of explanation is not immediately obvious.

Failure of a usually dominant gene to express itself in a heterozygous individual, as well as varying expression of the gene in different individuals is, of course, well known in human genetics. The ophthalmological data of the present paper provide evidence of the variable expression of the gene for aniridia. Among 16 aniridic persons who were examined by the authors, five were found to have small peripheral tags of iris, no tags being visible in the remaining 11 persons. Particular consideration is due the description of IV-26, a five-year-old son of an aniridic man. Although appearing grossly normal, more thorough examination showed that IV-26 has hypoplasia of the iris stroma, ectopia and dyscoria of the pupils, nystagmus, photophobia, and poor vision (6/30 − 1). There is, therefore, a strong presumption that this boy has the gene for aniridia but does not manifest the most characteristic feature of the pathological complex. If this is the case, the argument for non-penetrance as an explanation for the presence of the four aniridic individuals in Generation II is strengthened. However, as indicated in Table 1, the parents of Generation II are not known to have had any of the above-mentioned defects of IV-26.

In order to ascertain the frequency with which carriers of the gene for aniridia are described as being normal or nearly normal, a survey of the available literature was made, looking for descriptions of persons who are reported to have had an aniridic parent and an aniridic child. The results of this survey are summarized in Table 2. It is seen that only 13 persons were located who, with their parent and child, were

TABLE 2. TABULATION OF AVAILABLE DATA GIVING DESCRIPTIONS OF THE IRIDES OF PERSONS HAVING BOTH AN ANIRIDIC PARENT AND AN ANIRIDIC CHILD

Source	Number Aniridic	Number Not Aniridic	Remarks on Non-aniridic Individuals
All three generations medically examined			
Bell, 1932	5	1	Ped. 1104. Bilateral colobomata to margin of cornea.
Komai, 1934	1	0	
Neher, 1938	2	0	
Vogt, 1941	1	0	
Beattie, 1947	1	1	Slight bilateral irregularity in the pupillary margin, slight hypoplasia of iris stroma of left eye.
Møllenbach, 1947	1	0	
Total	11	2	
All three generations *not* medically examined			
Bell, 1932	23	2?	Pedigrees 1105 and 1130: descriptions seem uncertain.
Brooks, 1935	0	1?	Parent stated only to be "blind at early age."
Detroy and Bisiaux-Aufort, 1938	1	0	
Neher, 1938	2	0	
Vogt, 1941	1	0	
Beattie, 1947	9	0	
Pincus, 1948	5	0	
Schachter and Ourgaud, 1948	2	0	
Callahan, 1949	2	0	
Kříž, 1951	2	0	
Total	47	3?	

medically examined. Of these 13, two did not lack irides; one of these two persons had bilateral colobomata to the margin of the cornea and the other had slight bilateral irregularities in the pupillary margin and a slight hypoplasia of the stroma of the left iris. An additional 50 persons were located where all three generations were not medically examined and, of these, three were reported not to have aniridia. The reliability of the descriptions of two of these three persons is a matter of conjecture, being obtained indirectly from lay persons, while in the third case the person was ophthalmologically examined but the only information on the parent is that she was "blind at an early age."

It therefore seems established that a person may have the gene for aniridia and have almost normal irides or have only colobomata of the irides. The question of a person's having the aniridia gene and completely normal eyes remains unanswered. Several estimates of the penetrance of the gene may be calculated from the above data: Using only the 13 cases in which all three generations were examined, the pene-

trance with respect to clinically demonstrated aniridia (excluding colobomata and slight pupillary irregularities) is 11/13 or 0.846 ± 0.100, while if all cases are combined and treated as if reliable, the penetrance is 58/63 or 0.921 ± 0.034. The estimate of penetrance, defined as producing *any* congenital irregularity in the pupillary margin, is unity for the 13 completely examined cases but cannot be estimated from the 50 partially examined cases since slight abnormalities would probably not be recorded.

The alternative possibility, that of GM, is less obvious and in man, as well as in the extensively investigated domestic fowl (Hollander, 1944; Hutt, 1949), has not been demonstrated to occur. MacKenzie and Penrose (1951) suggested that GM occurred in one of their pedigrees of ectrodactyly, 3 of the 8 children of a normal person (with 2 normal spouses) being affected. Since the expression of ectrodactyly is known to be quite variable in some families and this family contains only 5 affected members, it is not possible to rule out non-penetrance as an alternative explanation. However, because of the similarity of expression of the trait in this pedigree to that in their other, much larger pedigree, which exhibited complete penetrance, they preferred the hypothesis of GM. Possible somatic mosaics, in contrast to gonadic mosaics, have been described in man (Zlotnikoff, 1945) and the fowl (Hollander, 1944; Hutt, 1949), as well as in many other organisms. Convincing evidence for the natural existence of mosaic gonads, shown by the production of two or more mutant offspring (having the same mutant character) from a single non-mutant parent (having one or more non-mutant mates), has been presented for *Drosophila melanogaster* (Bridges, 1919; Muller, 1920; Mohr, 1923; Morgan, Bridges, and Sturtevant, 1925), the guinea pig (Wright and Eaton, 1926), and the house mouse (Grüneberg, 1952; Dunn and Gluecksohn-Waelsch, 1953). Artificial production of gonadic mosaics has been reported in Drosophila, both by means of X-rays (Harris, 1929; Auerbach, 1950) and chemical mutagens (Auerbach, 1946, 1950). The proportion of mutated gametes, which, within statistical limits, is equal to half the proportion of gonad which is mutant, varies greatly; in the five cases in the mouse described by Grüneberg, the range is from 2 out of 63 tested gametes to 4 out of 9. The one case in the guinea pig produced 79 mutant gametes out of 228 tested, a proportion of 0.35.

A reliable estimate of the frequency of GM in mammals is not possible at present since the number of inspected animals is not known, but some data are available concerning the proportion of observed new mutations in the mouse known to have resulted from a mosaic gonad. Out of 9 genes listed by Grüneberg (1952) which first appeared in a laboratory as mutations and had easily visible effects in heterozygotes, 3 appeared in two or more progeny of a normal parent. As Grüneberg (1952) and Dunn and Gluecksohn-Waelsch (1953) point out, this form of mutation, in the mouse at least, may be more common than has been previously thought. Muller (1920) pointed out that the fact that a dominant mutation usually first manifests itself in one mutant individual, and not in a cluster of two or more, does not necessarily mean that, on a "per cell" basis, mutation is more likely in mature gametes than in cells of the early undifferentiated gonad. There are many more cells produced in late stages of gonadal development than in early, and the cells remain longer in the later stages. The usual observation—most mutants occurring singly—can result if mutations are as likely to occur at one stage as another.

It is pertinent at this point to survey the studies made on dominantly inherited traits in man to see whether evidence is available for demonstrating GM. The ideal proof will be the presence of more than one affected individual in the first (chronologically speaking) affected sibship, where the trait is inherited as a simple, rare, easily recognizable dominant with complete penetrance and uniform expression. A rare trait is preferable in order to minimize the effect of possible illegitimacy. This ideal situation does not yet exist and, in particular, there is a weakness in most studies in that there is no independent determination of penetrance and presence of more than one affected sib in the first affected sibship, the same data being used for both. Table 3 lists studies made on aniridia and other rare, dominant, highly penetrant traits, presenting data concerning the penetrance of the trait and existence of several affected individuals in the first affected sibship. It should be noted that two of the studies, Bell (1932) and Reese (1949), are based on surveys of the literature and, because of lack of uniformity of diagnosis and inclusion of very early reports, are therefore much less satisfactory than the other studies. These two studies contain the largest number of kindreds with several affected persons in the first affected sibship. The traits appearing to be most reliable for our purpose are chondrodystrophy and osteogenesis imperfecta, being recognizable at an early age and completely penetrant (in the osteogenesis imperfecta syndrome, blue sclerae, at least, being present), according to the studies quoted. Out of a total of 145 kindreds from these two studies in which the first affected sibship is known (i.e., the parents reported normal by the author), none was observed to have more than one affected member in the first affected sibship. This negative result makes GM as an explanation for Bell's data seem quite unlikely, assuming, as seems justified, that the proportion of germ cell mutations which occur early in the development of the zygote and give rise to two or more mutant offspring is approximately constant for different dominant genes. If perfect dominance and accurate diagnoses obtained in her data, the probability is less than 0.001 of obtaining the observed results of 3 kindreds out of 13 showing several affected in the first affected sibship and the corresponding figures of none out of 145 for chondrodystrophy and osteogenesis imperfecta. Therefore it appears that non-penetrance and/or misdiagnoses occurred in her data. The result of Reese (1949) seems less significant in view of the finding of Falls and Neel (1951) of a definite instance of non-penetrance of the gene for retinoblastoma. They had 71 kindreds in which the first affected sibship was known; two kindreds had two or more affected individuals in the first affected sibship, but here again non-penetrance is a definite probability.

Borberg's (1951) one kindred (No. 71), however, seems to offer more convincing evidence for GM in man, since, according to his study and that of Crowe, Schull, and Neel (unpublished) neurofibromatosis behaves as a regular dominant. Both parents of the first affected sibship were alive and reported normal at ages 79 and 71. The author examined each parent over the entire body without finding any café-au-lait spots (Borberg, 1953). There were only 16 persons in his study who had both a parent and a child affected with neurofibromatosis, but all 16 were themselves affected.

If chondrodystrophy and osteogenesis imperfecta are as regularly dominant as the studies of Mørch (1941) and Seedorff (1949) seem to indicate, the absence of evidence for GM in a total of 145 kindreds can be used to provide an estimate of the upper limit

TABLE 3. TABULATION OF STUDIES MADE ON ANIRIDIA AND OTHER TRAITS INHERITED AS RARE DOMINANTS OF HIGH PENETRANCE, WITH REGARD TO PENETRANCE AND PRESENCE OF FIRST-AFFECTED SIBSHIPS CONTAINING MORE THAN ONE AFFECTED INDIVIDUAL

Trait	Author	Penetrance*	No. of Kindreds in Which First Affected Sibship is Known	No. of Kindreds Having 2 or More Affected in First Affected Sibship	Remarks
Data from own research					
Aniridia	Møllenbach, 1947	See table 2	22	0	
Chondrodystrophy	Mørch, 1941	Unity?	98	0	No kindreds with more than 2 generations affected were observed. No skipping of generations observed.
Neurofibromatosis	Borberg, 1951	16/16	1	1	First affected sibship considered known only when both parents alive and reported normal. No. 71 is the aberrant kindred.
Neurofibromatosis	Crowe, Schull & Neel (unpub.)	11/11	29	0	Both parents examined and found normal. The affected individual was examined and often some or all of his sibs.
Osteogenesis imperfecta	Seedorff, 1949	37/37	47	0	Blue sclerae, with or without fractures, were considered to indicate the presence of the gene for the osteogenesis imperfecta syndrome.
Retinoblastoma	Falls & Neel, 1951	?	71	2	Only one 3-generation kindred. A case of definite non-penetrance was found in this study. Kindred #71 not counted. Nos. 4 and 35 are the aberrant kindreds.
Data from survey of literature					
Aniridia	Bell, 1932	See table 2	13	3	Nos. 1099, 1124, & 1134 are the three aberrant kindreds. In 1099 both parents of the first affected sibship were examined; one had corneal opacities, strabismus and nystagmus. Not known whether the parents of other two kindreds were examined; they were reported normal.
Retinoblastoma	Reese, 1949	Not given	605	7	No details given.

* When 3-generation data are available the penetrance is estimated by the following fraction: $\frac{\text{No. persons with both an affected child and an affected parent who are themselves affected}}{\text{No. persons with both an affected child and an affected parent}}$

of the proportion of all mutations which give rise to two or more affected sibs in first affected sibships. It is found that when this proportion is 0.031 the results observed in the 145 kindreds—one mutant per first affected sibship—will occur once in a hundred times. Therefore the proportion of mutations which give rise to detectable clusters of mutants is probably less than 3 per cent. If this order of magnitude is correct, it is not surprising that there is little convincing evidence for GM in man.

The fact that among the human dominant traits known to have mutated several times, there are none which can be proved with considerable statistical confidence to have a non-penetrance rate of less than 3 per cent, makes it unlikely that convincing proof for GM will appear in the immediate future. We must conclude that the original question prompting this discussion must remain unanswered; non-penetrance and GM are both possible explanations for the presence of four aniridic individuals in the first affected sibship of the kindred described in this paper. The known existence of GM in the mouse and guinea pig, however, makes it worthwhile to keep this possibility in mind when situations similar to the one described occur.

SUMMARY

A kindred containing 23 cases of congenital aniridia distributed in four generations was studied. Complete ophthalmological examinations were performed on 20 affected individuals and 38 of their normal relatives. Except for one probable case of incomplete expression the gene determining aniridia in this kindred appears to behave as a dominant of high penetrance. No linkage between the locus for aniridia and the loci for the MN and Rh blood groups could be demonstrated. Data concerning linkage with the ABO blood group locus were not informative.

The first occurrence of aniridia was in a sibship containing four affected and six normal individuals. This appearance of aniridia in several children of an apparently normal couple is interpreted to be due to the occurrence, in one of the parents, of either non-penetrance of the gene for aniridia or to germinal mosaicism (GM) (gonad composed of normal and mutant tissue). It was not possible to decide between these two alternatives.

Documented cases of GM are known in the mouse but none is definitely known in man. However, a survey of certain well-studied rare dominant traits revealed some evidence for the occurrence of GM in man. This survey further indicated that the proportion of human dominant mutations which produce a cluster of mutant individuals (two or more mutant children from normal parents) is probably less than 3 per cent. Conclusive evidence for GM in man, therefore, may not become available for some time to come.

REFERENCES

AUERBACH, C. 1946. Chemically induced mosaicism in *Drosphila melanogaster*. *Proc. R. Soc. Edinburgh*, 62: 211–222.

AUERBACH, C. 1950. Differences between effects of chemical and physical mutagens. In: Gli agenti mutageni. *Pubbl. Staz. zool. Napoli*, 22 (Supplement).

BEATTIE, P. H. 1947. A consideration of aniridia, with a pedigree. *Brit. J. Ophth.* 31: 651–676.

BELL, J. 1932. Anomalies and diseases of the eye. *Treasury of Human Inheritance*, Vol. 2. Cambridge, England: University Press.

BORBERG, A. 1951. Clinical and genetic investigations into tuberous sclerosis and Recklinghausen's neurofibromatosis. *Opera ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis*, Vol. 23. Copenhagen: Ejnar Munksgaard.

BORBERG, A. 1953. Personal communication.

BRIDGES, C. B. 1919. The developmental stages at which mutations occur in the germ tract. *Proc. Soc. Exp. Biol.*, 17: 1–2.

BROOKS, H. L. 1935. An interesting case of aniridia. *Eye Ear & c. Month.*, 14: 62–63.

CALLAHAN, A. 1949. Aniridia with ectopia lentis and secondary glaucoma. *Am. J. Ophth.*, 32: 28–40 (pt. 2).

DETROY, L. AND BISIAUX-AUFORT, MME. 1938. A propos de deux cas d'aniridie congénital et familiale. *Echo méd. nord.*, 9: 465–467.

DUNN, L. C. AND GLUECKSOHN-WAELSCH, S. 1953. Genetic analysis of seven newly discovered mutant alleles at locus T in the house mouse. *Genetics*, 38: 261–271.

FALLS, H. F. AND NEEL, J. V. 1951. Genetics of retinoblastoma. *Arch. Ophth., Chic.*, 46: 367–389.

FINNEY, D. J. 1940. The detection of linkage. *Ann. Eugen., Lond.*, 10: 171–214.

FINNEY, D. J. 1942. The detection of linkage. V. Supplementary tables. *Ann. Eugen., Lond.*, 11: 224–232.

GRÜNEBERG, H. 1952. The genetics of the mouse. *Bibliogr. genet., Gravenh.*, XV.

HALDANE, J. B. S. 1949. The rate of mutation of human genes. Proc. 8th Inter. Congr. Genetics, *Hereditas, Lund*, Suppl. Vol., 267–273.

HARRIS, B. B. 1929. The effects of ageing X-rayed males upon mutation frequency in Drosophila. *J. Hered.*, 20: 299–302.

HOLLANDER, W. F. 1944. Mosaic effects in domestic birds. *Q. Rev. Biol.*, 19: 285–307.

HUTT, F. B. 1949. *Genetics of the Fowl.* First ed. New York: McGraw-Hill Book Co., Inc.

KOMAI, T. 1934. Contributions to the genetics of the Japanese race. I. Pedigrees of hereditary diseases and abnormalities found in the Japanese race. Tokyo: Maruzen Co.

KŘÍŽ, R. 1951. Vrozena aniridie. *Voj. zdrav. listy.*, 20: 223–225.

MACKENZIE, H. J. AND PENROSE, L. S. 1951. Two pedigrees of ectrodactyly. *Ann. Eugen., Lond.*, 16: 88–96.

MOHR, J. 1953. A study of linkage in man. *Opera ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis*, Vol. 33. Copenhagen: Ejnar Munksgaard.

MOHR, O. L. 1923. A somatic mutation in the singed locus of the X-chromosome in Drosophila melanogaster. *Hereditas, Lund*, 4: 142–160.

MØLLENBACH, C. J. 1947. Congenital defects in the internal membranes of the eye. *Opera ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis*, Vol. 15. Copenhagen: Ejnar Munksgaard.

MØRCH, E. T. 1941. Chondrodystrophic dwarfs in Denmark. *Opera ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis*, Vol. 5. Copenhagen: Ejnar Munksgaard.

MORGAN, T. H., BRIDGES, C. B. AND STURTEVANT, A. H. 1925. The genetics of Drosophila. *Bibliogr. genet., Gravenh.*, II: 1–262.

MULLER, H. J. 1920. Further changes in the white-eye series of Drosophila and their bearing on the manner of occurrence of mutation. *J. Exp. Zool.*, 31: 443–472.

NEHER, E. M. 1938. Aniridia congenita, irideremia. *Am. J. Ophth.*, 21: 293–298.

PINCUS, M. H. 1948. Aniridia congenita. *Arch. Ophth., Chic.*, 39: 60–66.

REESE, A. B. 1949. Heredity and retinoblastoma. *Arch. Ophth., Chic.*, 42: 119–122.

SCHACHTER, M. AND OURGAUD, A. G. 1948. Trois observations d'aniridie. *Arch. opht., Par.*, 8: 382–389.

SEEDORFF, K. S. 1949. Osteogenesis imperfecta. *Opera ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis*, Vol. 20. Copenhagen: Ejnar Munksgaard.

SORSBY, A. 1951. *Genetics in Ophthalmology.* London: Butterworth & Co., Ltd.

VOGT, A. 1941. Erbverbundenheit des abblendungsapparates und der Makulafunction des Menschen. *Schweiz. med. Wschr.*, 71: 432–433.

WAARDENBURG, P. J. 1932. *Das menschliche Auge und seine Erbanlagen.* The Hague: Martinus Nijhoff.

WRIGHT, S. AND EATON, O. N. 1926. Mutational mosaic coat patterns of the guinea pig. *Genetics*, 11: 333–351.

ZLOTNIKOFF, M. 1945. A human mosaic. *J. Hered.*, 36: 163–168.

A New Syndrome of Anomalies in Mice and a Possible Human Counterpart[1]

WALTER C. MORGAN, JR.

South Dakota State College, College Station, South Dakota

IN REPORTING a series of developmental anomalies attributed to the Crooked tail mutation, symbol *Cd*, in the house mouse (10) it was observed that many of them resembled human anomalies which had hitherto been considered unrelated. The associated abnormalities in the surviving homozygotes were concerned with the axial skeleton, the integument, the urogenital system and the central nervous system. Table 1 compares the abnormalities observed in SMALL (*Cd/Cd*) mice and humans with status Bonnevie-Ullrich. However, less than 30% of the *Cd/Cd* embryos survive. Analyses of findings from dissected Crooked females accounted for approximately 64% of the remaining homozygotes: 24% as preimplantation deaths, 24% as postimplantation deaths and 16% dying perinatally as monsters with anencephaly.

The present report does not include a detailed discussion of cases of preparturitional death of early human fetuses which could fall into the two categories referred to as preimplantation deaths and postimplantation deaths. Syndrome analogies of two morphological representatives of the *Cd/Cd* genotype (exencephaly and status SMALL) are compared with the human anomalies anencephaly and status Bonnevie-Ullrich in an effort to emphasize their many similarities. It is hoped that human geneticists will in the future, be aware of the possibility that a common genotype may initiate one, or both, of these anomalies, and that they will organize their data from human pedigrees in a manner which will help to prove or disprove this hypothesis.

MOUSE EXENCEPHALY VS. HUMAN ANENCEPHALY

The exencephaly of Crooked tail homozygotes appears to be the same as the pseudencephalic condition reported by Snell and Picken (13) and by Bonnevie (1). In their studies of more than 100,000 deliveries in Sweden, Böök and Rayner (2) reported 67 cases of anencephaly, which they acknowledged as being, "closely related to pseudencephaly in the mouse." Data indicating that early death of the embryos often was associated with congenital derangements, such as craniorhachischisis and accompanying spina bifida, led them to conclude that anencephaly is probably initiated by a genetic unit (viz. that there is a gene for anencephaly in humans). They found that 50% of the anencephalic cases studied could be classified as having reached a full term development; at least 10% resulted in spontaneous abortions occurring near the end of the gestational period, and the rest were born prematurely. All exencephalic *Cd* homozygotes, ranging from 11 days to 19 days gestational age were alive

Received August 16, 1953.

[1] A portion of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in the Department of Genetics at The University of Connecticut.

TABLE 1. ANOMALIES COMMON TO STATUS SMALL AND STATUS BONNEVIE-ULLRICH

Cd/Cd Mice*	Reported by	Human Bonnevie-Ullrich
Abnormal pelage	Turner, Ullrich	pterygium colli
Skeletal deformities	Turner	cubitus valgus
Sexual underdevelopment	Turner	sexual underdevelopment
Retarded growth	Ullrich, Turner	dwarfism
Unilateral kidney absence	Dreyfus	kidney anomaly
Inclined pinna	Cotterman & Falls	displaced external ear
Non-eruption of lower incisors	Cotterman & Falls	poor dentition
Bent nose	Cotterman & Falls	unilateral nose deformity
Abnormal eyes	Cotterman & Falls Pfändler	eye abnormalities

* Reported by Morgan.

at dissection, indicating that exencephaly *per se* did not cause early embryonic death in the mice. Böök and Rayner also observed a hydroamniotic condition in 33 cases which they interpreted as a consequence of the pathological condition of the fetus. Similarly a hemorrhagic appearance of the amniotic fluid in *Cd* exencephalics appeared to be caused by a rupture of one or more cephalic blood vessels at approximately the eighteenth day. Posterior spina bifida was particularly looked for in newborn and in dissected *Cd/Cd* embryos. No spina bifida aperta was found, and only two mild cases of spina bifida occulta were observed in cleared adult specimens. In the light of previous recorded relationships of posterior spina bifida to tail anomalies (4) (6) this was surprising.

Feuerlicht (7) stated that in general human anencephalic fetuses were born alive but expired shortly after birth. This was certainly true of the *Cd* exencephalics. She discussed the probability of a mother who has had one anencephalic embryo giving birth to a second. Indications of low probability that a mouse which has delivered an acranial embryo (a postnatally denuded exencephalic) will have more acranials in subsequent litters are presented in table 2. Feuerlicht quotes Quigley as stating that "... in these cases of autopsied anencephalics absence of the pituitary gland and aplasia or hypoplasia of the adrenal glands have been noted." All *Cd* exencephalics possessed adrenals which appeared macroscopically normal. Grossly normal appearing pituitary glands were observed on the brains of five dissected surviving homozygotes.

Warren (16) made a study of nine human acranial fetuses with total or subtotal anencephaly. He reported that the existence of a brain anlage was indicated by the complete development of the eyes in all specimens (which was also true for the *Cd* exencephalics) and the presence of the trigeminal, vagus and hypoglossal nerves. He concluded that whatever the underlying cause of anencephaly, it probably did not affect the developing brain before late in the third, or early in the fourth week of intrauterine life (i.e. until after the optic vesicles appeared). Bonnevie (1) concluded that the processes which terminate in pseudencephaly were initiated at the seventh or eighth day; this is in animals whose entire gestational period is 19 days.

Patten (11) recently suggested that the disturbances in brain development may

TABLE 2. REPEATED RECOVERY OF ACRANIAL EMBRYOS FROM KNOWN TRANSMITTERS

Female	Litters	Total Born	Normal Tail	Crooked Tail	Acranial Head
663	1	6	1	2	1
1243	2	12	5	7	0
1282	1	5	3	2	0
1665	1	4	2	2	0
1691	3	17	7	10	0

have as an underlying factor a local overgrowth. In his studies of human specimens with abnormal heads he found that local portions of the walls of the neural tube were richly plicated as if they had grown too large for the space in the head which they were destined to occupy. In some cases the redundant brain walls caused the head to become high-crowned; in others the overgrown brain protruded as an encephalocoele.

STATUS SMALL (MICE) VS. STATUS BONNEVIE-ULLRICH (HUMAN)

Again reference is made to table 1. Although the most frequently expressed anomalies of the surviving retarded Small homozygotes are concerned with the axial skeleton, pleiotropic effects are manifested in the central nervous system (nervous head movements[2]), the integument (non-eruption of the lower incisors and abnormal pelage) and the urogenital system (occasional kidney absence). The nervous head movement of Smalls and the motor disturbances of the cranial nerve region demonstrated in humans (15) are not included as analagous conditions in table 1 because there is some doubt as to their relation to each other.

Human cases which seem to parallel most nearly the *Cd* Small phenotype are found in the so-called "status Bonnevie-Ullrich" (12) which is apparently synonymous with "Turner's syndrome" (14). As in the case of anencephaly (2) many more abnormal females have been reported than males. Ullrich (15) reported that pterygium colli and its numerous allied anomalies was almost invariably associated with dwarfness and conspicuous infantilism in older female patients. The dwarfness showed some distinct clinical differences from that of pituitary dwarfness. This was also true when comparing *Cd* Small mice with mice homozygous for the gene responsible for pituitary dwarfism. Treatment with pituitary growth hormones did not stimulate growth in individuals suffering from status Bonnevie-Ullrich.

Kaven (8) reported a short-tailed anomaly of the house mouse which was accompanied by hemorrhagic blebs (blood blisters) and vertebral deformities. The females seemed to be more severely affected. (Quantitatively many more females have been variously reported as having anencephaly, and similar deformities, than have males.) Hemorrhagic blebs have not been observed in autopsies of 640 F_2 embryos from two heterozygous Crooked tail parents. In comparing Kaven's mutants with the Klippel-Feil syndrome, Ullrich (15) stated that "All of these developmenal anomalies of the axial skeleton are nevertheless far removed from the anomaly complex of *my* (myelencephalic bleb) mice, and are presumably brought about through entirely different

[2] Nervous head movements are rapid, successive jerkings of the head in a vertical plane.

pathogenic events." This statement has certainly been invalidated by the observations reported with *Cd*. In these the exencephalic and small phenotypes have been shown to be dependent upon the homozygous state of *Cd*, a mutation which manifests itself in only skeletal abnormalities in the heterozygote. Ullrich also mentioned that the kidney anomaly in Dreyfus' case need not be related to the syndrome. If status Small is comparable to status Bonnevie-Ullrich, observations of kidney deficiencies in *Cd* homozygotes increase the probability that kidney defects may be associated with the human syndrome.

In their study of unilateral developmental anomalies, found in sisters, Cotterman and Falls (3) reported several irregularities which have also been observed in *Cd* Small mice. The left external ear of the individual referred to as A-5 was located ventrad to its normal position; several Small mice have been observed with inclined pinna. A-5 also had a left-sided deformity of the nose; a "bent nose" condition has been observed in some *Cd* Smalls. The seven year old sister, A-6, lacked the anterior upper teeth; Small mice lack eruption of the lower incisors.

DISCUSSION

Thus, the observed manifestations of the Crooked tail mouse homozygotes demonstrate several phenomena which heretofore have been treated as unrelated in human studies. The pleiotropic effect of *Cd/Cd* is expressed by giving rise to exencephalics (comparable to the series of brain anomalies reported as acrania, anencephaly, rhachischisis, craniorhachischisis, holocrania, etc. in humans) and to a phenotype which appears to be comparable to the human "status Bonnevie-Ullrich." In addition to these expressions, prenatal death (as calculated from embryological studies) has accounted for more than 50% of the *Cd/Cd* zygotes. If the suggestion of Böök and Rayner (2) that there is a genetic precursor for anencephaly is an actuality, then the study of *Cd* homozygotes may provide clues for further analyzing human pedigrees and accounting for many more of the homozygotes. This hypothesis is favored by the statement of Dunn's (5) that "the abnormal processes are themselves orderly and appear to be determined by the same rules which condition normal development."

It is recognized that two major barriers present themselves. The first is the difficulty of carrying out complete human pedigree analyses and the impossibility of accumulating autopsy data from all abnormal individuals. Thus, an associated kidney deficiency, which has been observed in only 2% of the surviving *Cd/Cd* mice, would be difficult to perceive. And, more dramatically, the carefully analyzed skeletal abnormalities in the mice could not hope to be put on a comparative basis in human studies, even by employing X-ray techniques. The second point which is difficult to evaluate is the influence of modifiers in the Crooked tailed stock. Hybridization experiments (9) have already indicated that dominant modifiers can diminish the expressivity of tail crooks and the non-eruption of lower incisors.

SUMMARY

Mice homozygous for the Crooked tail mutation (*Cd*) may: (1) die soon after fertilization, (2) die late in embryogeny, (3) die at birth as exencephalics, or (4) survive as Smalls. It is postulated that heretofore unrelated human anomalies may have a similar common genetic basis.

REFERENCES

1. BONNEVIE, K. 1936. Pseudoencephalie als spontane recessive (?) Mutation bei der Hausmaus. Skr. Norske Vidensk.-Akad. Oslo, *Mat.-nat. Kl.* 9: 1–39.
2. BÖÖK, J. A. AND RAYNER, S. 1950. A clinical and genetical study of anencephaly. *Am. J. Hum. Gen.* 2: 61–84.
3. COTTERMAN, C. W. AND FALLS, H. F. 1949. Unilateral developmental anomalies in sisters (status Bonnevie-Ullrich). *Am. J. Hum. Gen.* 1: 203–213.
4. CREW, F. A. E. AND AUERBACH, C. 1941. Pigtail, a hereditary tail abnormality in the house mouse, Mus musculus. *J. Genet.* 41: 267–274.
5. DUNN, L. C. 1949. Some relations between mutations and abnormal development. *Bar Harbor Lectures.*
6. DUNN, L. C. AND GLUECKSOHN-SCHOENHEIMER, S. 1947. A new complex of hereditary abnormalities in the house mouse. *J. Exp. Zool.* 104: 25–51.
7. FEUERLICHT, N. 1950. Recurrent anencephaly. *J. Am. Med. Assn.* 143.
8. KAVEN, A. 1943. Das Auftreten einer Wirelsaulenanomalie bei der weissen Maus. *Erbarzt* 11: 49–54.
9. MORGAN, W. C. 1953. Crooked II. Increasing viability of homozygotes through hybridization. *Genetics* 38: 678.
10. MORGAN, W. C. 1954. A new Crooked tail mutation involving distinctive pleiotropism. *J. Genet.* 52: 354–373.
11. PATTEN, B. M. 1952. Overgrowth of the neural tube in young human embryos. *Anat. Rec.* 113: 381–393.
12. PFÄNDLER, U. 1952. L'ontogenie et l'hereditie du caputobstipum (torticolis congenital). *J. Génètique Humaine* 1: 169–185.
13. SNELL, G. D. AND PICKEN, D. I. 1935. Abnormal development in the mouse caused by chromosome unbalance. *J. Genet.* 31: 213–235.
14. TURNER, H. H. 1938. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. *Endoc.* 23: 566–573.
15. ULLRICH, O. 1949. Turner's syndrome and status Bonnevie -Ullrich. *Am. J. Hum. Gen.* 1: 179–202.
16. WARREN, H. S. 1951. Acrania induced by anencephaly. *Anat. Rec.* 111: 653–668.

Split-Hand with Unusual Complications

JOHN B. GRAHAM[1] AND CARL E. BADGLEY[2]

RECENT publications have emphasized that inherited skeletal anomalies of the extremities tend to remain constant in a single pedigree (Birch-Jensen 1949, Falls 1953, Johnston and Davis 1953). This has been interpreted as meaning that many are due to single gene substitutions. The concept has apparently evolved from studying small pedigrees, with laudable attempts at subdividing the anomalies into the simplest possible syndromes. The split-hand, or "lobster claw", deformity is considered one of the more specific of these skeletal defects. In the pedigree described below, the anatomic defect probably should be considered split-hand because the right hand of every affected person is deformed by some variation of this anomaly. However, some of the affected persons have additional deformities. The two probands, for example, have additional deformities of a severe type which are quite uncommon, judging by the literature. Their anomalies are so complex that one wonders whether defining split-hand as a discrete entity is not an oversimplification. In addition to the unusually severe complications, problems have arisen in interpreting the mode of inheritance.

THE AFFECTED FAMILY AND METHOD OF STUDY

A pedigree of split-hand in a large Michigan kindred of predominantly German extraction was ascertained twice. The two probands, related as cousins, were admitted on separate occasions to the University of Michigan Hospital for orthopedic evaluation and treatment. Investigation of the family revealed four additional affected persons, including one parent of each proband. Altogether, information was obtained on 165 persons. This included everyone who had lived in the United States and on whom reliable information was available. Particular attention was paid to possible consanguinity.

We examined four of the six affected individuals, and obtained roentgenograms on all six. Also, roentgenograms of upper and lower extremities (anterior-posterior and lateral) were obtained on four unaffected siblings of the last unaffected generation in the common line of descent. Two of these were parents of affected persons and the other two were aunts. Similar studies were made of the extremities of one individual (V, 23) with pes cavus, the youngest child in the consanguineous mating: IV, 9 with IV, 35.

RESULTS

Inheritance

The pedigree is shown in Figure 1, and probands are indicated by the conventional arrows. It should be noted that the disease was unknown in the family until

Received September 14, 1954.

[1] *Visiting Investigator, Heredity Clinic, Institute of Human Biology, University of Michigan, Ann Arbor; Associate Professor of Pathology, University of North Carolina, Chapel Hill.*

[2] *Professor of Surgery, University of Michigan, Ann Arbor.*

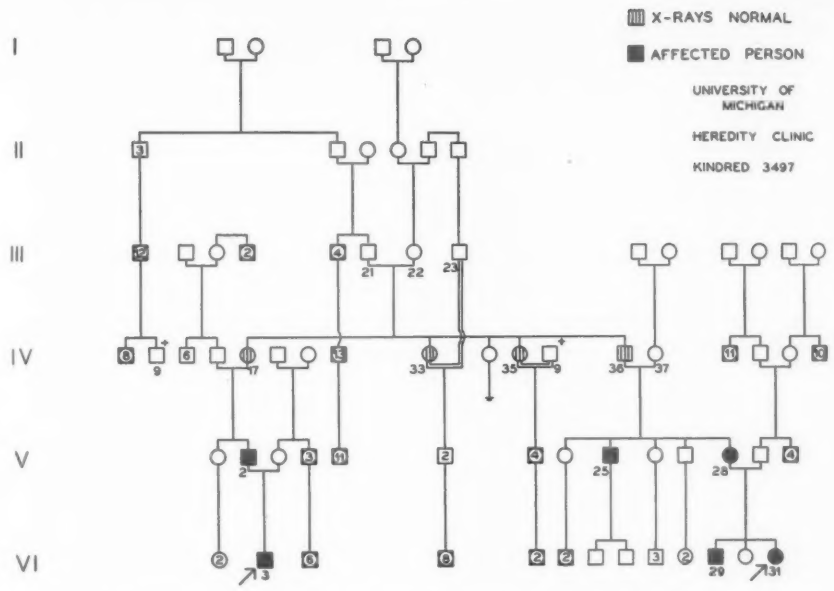


FIG. 1. A pedigree of split-hand. (+) indicates a man who is represented twice in generation IV, the male in a consanguineous mating.

generation V. Careful study uncovered no skeletal deformities among the members of generation IV. The ancestors common to the two lines of descent, III, 21 and 22, were reliably reported as unaffected. Each affected individual of generation VI has an affected parent in generation V, and the anomaly is unrelated to sex.

Description of Affected Individuals

V, 28: a 32-year-old housewife, is the oldest affected member of the family. Married in her early twenties, she has had three children, two with skeletal defects. Her right hand is a classical example of the "lobster claw", and there is hypoplasia of the first ray, right foot. These lesions are shown in the X-rays of Figure 2, A and B. The hand deformity is a very slight handicap as she performs all manner of housework without difficulty.

V, 25: a 30-year-old veterinarian, is the brother of V, 28. He could not be examined, but the X-rays of Figure 2, C and D show bilateral split-hand. His lower extremities are normal, and he has two normal sons.

V, 2: a 31-year-old implement dealer, is the first cousin of V, 25 and V, 28. He has a variety of split-hand on the right which is shown radiologically in Figure 2, E, but his lower extremities are normal. His only child, VI, 3, is described below.

VI, 29: 8-year-son of V, 28, has a right split-hand as shown in Figure 2, F. He has no other skeletal deformity and is an active, intelligent schoolboy.

VI, 31: 3-month-old girl, is the second daughter and third child of V, 28. At birth, after a normal pregnancy and easy delivery, severe deformities of both upper

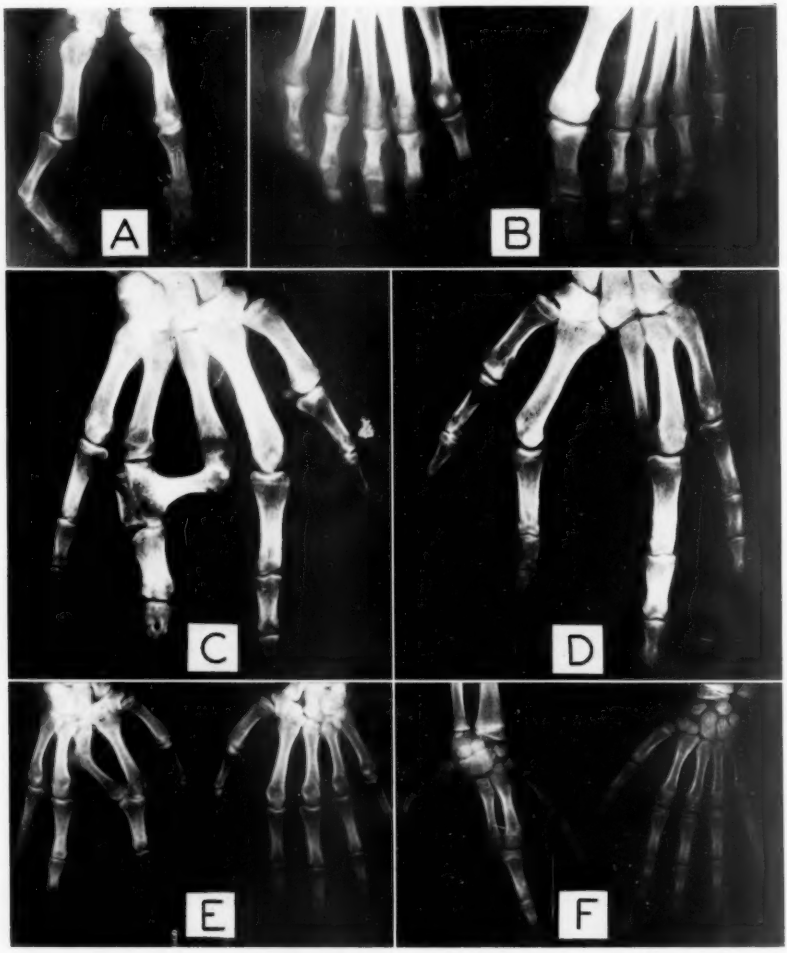


FIG. 2. Roentgenograms of the skeletal defects in four of the six affected persons: A. Right hand of V, 28. B. Feet of V, 28. C. Right hand of V, 25. D. Left hand of V, 25. E. Both hands of V, 2. F. Both hands of VI, 29.

extremities were noted. These, shown in Figure 3, A and B, include bilateral absence of the ulnae with radial dislocation at the right elbow, absence of three rays of the left hand and four on the right. Also, there is failure of ossification of the distal portion of the right clavicle with pseudoarthrosis in the midportion. This young girl will probably have a moderately functional hand on the left, but the right upper extremity will never be very useful.

VI, 3: 19-month-old son of V, 2, was born normally after an uneventful full term

delivery. It was noticed at birth that he had a split-hand on the right (Figure 3, C) and severe bilateral leg deformities. His leg deformities (Figure 3, D) include bowing and shortening of the right femur with congenital dislocation and acetabular changes, bilateral absence of fibulae, missing tarsals, metatarsals, and phalanges

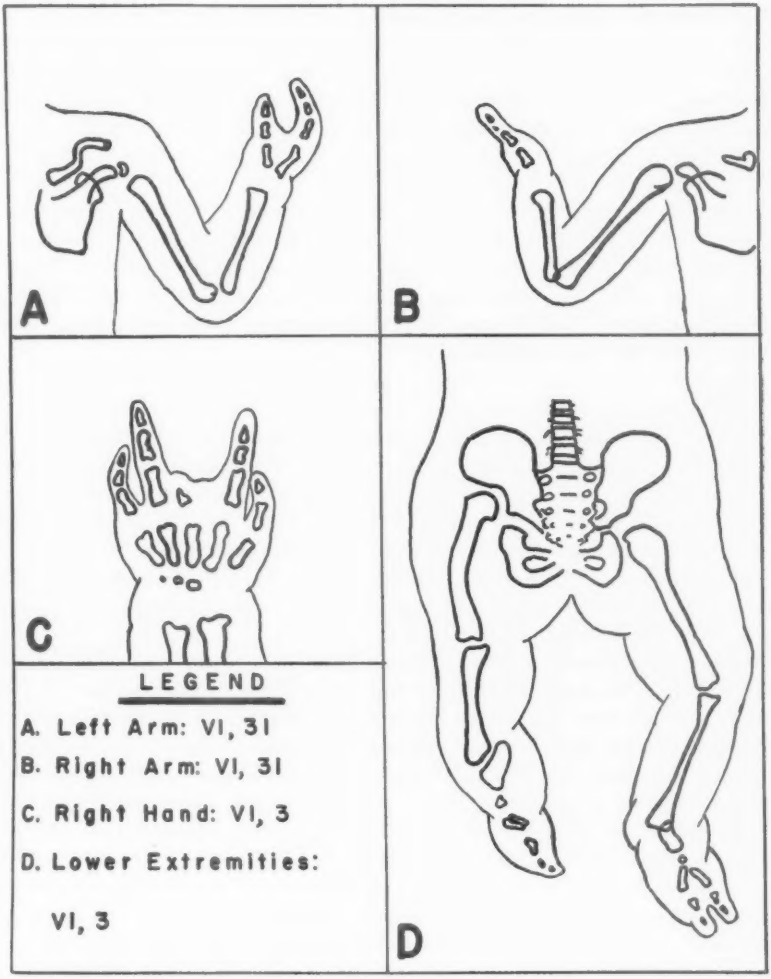


FIG. 3. Line drawings were prepared from numerous photographs and roentgenograms of the severely affected infants, VI, 3 and VI, 31 to show the multiple defects. The absence of ulnae, missing rays, and incomplete ossification of the right clavicle of VI, 31 are shown in A and B. The split-hand and absence of fibulae of VI, 3 with bowing and dislocation of the right femur and missing foot rays can be seen in C and D.

bilaterally, and club feet. These deformities will necessitate bilateral amputation at the knee eventually. A stable and usable left leg will probably be obtained, but the outlook is poorer on the right.

Studies on Possible Transmitters

A glance at the pedigree shows that two apparently normal siblings might have transmitted a crippling mutant gene to their children, that is, IV, 17 to V, 2, and IV, 36 to V, 25 and 28. The upper and lower extremities of these parents and two of their sisters, IV, 33 and IV, 35 were X-rayed seeking mild expression of such a gene. No evidence of a skeletal defect was found.

Consanguinity

Information was obtained on 78 marriages in the kindred. Two instances of cousin marriage were discovered, IV, 9 to IV, 35 and III, 23 to IV, 33. Two of the children of IV, 9 and IV, 35 had congenital cataracts removed in childhood. One (V, 23) has pes cavus in addition, but no abnormalities of the split-hand or split-foot type resulted from the cousin marriages. Also, consanguinity is not present in the matings which produced the affected persons.

DISCUSSION

Split-hand, or "lobster claw", is an uncommon hereditary abnormality of the upper extremity occurring in humans, apes, and Old World monkeys (Pearson 1931). The best estimate of the incidence in humans is that of Birch-Jensen (1949) who reported 1 case in 90,000 births in Denmark and 1 in 112,000 in the general population. Although the majority of cases in the Danish survey were sporadic, extensive pedigrees suggest that the defect is usually transmitted as a Mendelian dominant (Anderson 1886, Fotherby 1886, Lewis and Embleton 1908, Poponoe 1937, Hedgekatti 1939, MacKenzie and Penrose 1951).

Most writers have noted the variable expression of the split-hand gene; involvement of either or both hands are often seen in an affected sibship. The degree of penetrance is less clear. There has been no lack of penetrance in most of the large pedigrees (Anderson 1886, Fotherby 1886, Lewis and Embleton 1908, Hedgekatti 1939, MacKenzie and Penrose 1951). However, in Scott's pedigree (1933), one female in the fourth generation was reported as unaffected although having an affected parent and an affected daughter. In another pedigree of five generations with evidence of "skipping" (Johnston and Davis 1953), the authors noted carefully that the unaffected woman had "high foot arches". This tempts one to speculate over the significance of the pes cavus which we observed in V, 23.

The usual complications associated with split-hand are: split-foot in 50 per cent of cases, syndactyly, and webbing of fingers (Lewis and Embleton 1908, Poponoe 1937, Bauer and Bode 1940, Birch-Jensen 1949, Johnston and Davis 1953). Recent authors have commented that other complications are rare (Birch-Jensen 1949, Johnston and Davis 1953), and that the lesion, while disfiguring, is not particularly disabling. Bauer and Bode (1940), quoting studies of Rohlederer and Perthes, note that serious (unspecified) complications are seen occasionally.

The split-hand deformity in our pedigree is the most common but least serious

manifestation in the syndrome. With the exception of the small girl (VI, 31) who has only a single ray in the right hand, all of these individuals have functional, though deformed, hands. It should be emphasized that a larger assortment of bones have been involved in this pedigree than in any other which we have found in the literature. The clavicle, femur, ulna and fibula as well as the more usual carpals, tarsals, metacarpals, metatarsals and phalanges have been affected in one or another person. By way of comparison, Birch-Jensen found only two examples of involvement of the long bones among his 36 probands.

Although the defect in this family plainly has a genetic basis, certain interesting problems arise when one attempts a detailed explanation. The segregation ratio in generation VI, the presence of affected males and females, and the absence of consanguinity in the critical matings all suggest a dominant type of inheritance. However, the appearance of the defect in two lines of descent in the same generation without affected antecedents, invalidates the hypothesis of a single, completely penetrant, dominant gene. It is interesting to note that three of Birch-Jensen's pedigrees (numbers 1, 5, 6) presented similar problems.

The distribution of affected persons in our pedigree might have resulted either from a dominant gene with reduced penetrance or multiple mutation. Conclusive evidence for either hypothesis is lacking at present. The literature indicates that the gene for split-hand is highly penetrant in most pedigrees. However, as noted earlier, clinical evidence suggests that our pedigree is not the usual type. We have not attempted to estimate the penetrance of the split-hand gene from the pedigrees in the literature for comparison with ours because of this possibility of heterogeneity. It is possible that future additions to our pedigree will show undoubted "skipping". If observed, this will greatly increase the probability that the gene had been present but not penetrant in preceding generations. It will be important to maintain contact with the family, particularly to examine the progeny of the unaffected children of generations V and VI.

Multiple mutation is a possibility which should be considered. Such an event in our pedigree might have taken the form of three independent mutations. An alternative possibility is two independent mutations, one occurring very early in the development of a gonad causing it to be mosaic for normal and mutant tissue, and resulting in the occurrence of the two mutant individuals in one sibship: V, 25 and 28. Interestingly, MacKenzie and Penrose (1951) have reported a large pedigree of ectrodactyly in which such a "cluster" mutation may have been encountered. The frequency of "cluster" mutation in man is to be discussed in detail by Reed and Falls in a paper in press. These authors have allowed us to use their estimate of the frequency of this phenomenon in man for the calculations below.

Making the assumptions, (1) that Birch-Jensen's estimate of the birth incidence (1:90,000) is the upper limit for the mutation frequency, and (2) that the Reed and Falls estimate of 1:33 is the upper limit of the proportion of all mutations which produce detectible gonadal mosaics in man, and (3) that 7:12 is the upper limit of the proportion of all cases of split-hand which are sporadic and presumably mutations (Birch-Jensen 1949), it is apparent that either of the mutational possibilities is, at best, unlikely.

More specifically we may estimate: (1) the probability, given an ascertainment

through an affected person, that his affected parent will have been a sporadic case (presumably a mutation), and that two other mutations will have occurred in a collateral line of descent; also, (2) the probability, given an ascertainment through an affected person, that his affected parent will have been a sporadic case and that a gonadal mosaic mutation will have occurred in a collateral line. The first probability would be $(7/12)(1/90{,}000)^2$ and the second $(7/12)(1/33)(1/90{,}000)$.

Comparing this pedigree with those in the literature has made us suspect that there are several genes which may cause the typical split-hand deformity. It is possible that the mutant gene in our pedigree is less common, less penetrant and considerably less innocuous than the majority of those previously described.

From the standpoint of clinical medicine and genetic counseling, the important feature of this pedigree is the unusually serious nature of the deformities in the sixth generation. These defects are certain to cause undesirable social and economic dislocations in the immediate family groups. It would appear wise for the counselor to recognize that an occasional pedigree of split-hand will produce unpleasant surprises if he adopts a casual attitude toward the possible complications, an attitude which the literature at present encourages.

SUMMARY

A pedigree of split-hand in a large Michigan family is described. The accompanying complications are unusually severe, and the distribution of affected individuals poses problems in interpreting the mode of inheritance.

It is suggested that there may be several genes responsible for the split-hand deformity, and that the one responsible for this pedigree is rarer and of more serious import than the majority of those previously reported.

REFERENCES

ANDERSON, W. 1886. "Congenital Malformations of the Hands and Feet Transmitted through Four Generations", *Brit. M. J.*, 1: 1107–1108.

BAUER, K. K. AND BODE, W. 1940. "Spalt-hand und Spalt-fuss", Handbuch der Erbbiologie des Menschen, Vol. 3, Part 1, 257–260. Julius Springer, Berlin.

BIRCH-JENSEN, A. 1949. "Congenital Deformities of the Upper Extremities", Opera ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis, 19: 1–285.

FALLS, H. F. 1953. "Skeletal System, Including Joints", in "Clinical Genetics", Arnold Sorsby (ed.), Butterworth and Co. (Publishers) Ltd., London, 236–286.

FOTHERBY, H. A. 1886. "The History of a Family in Which a Similar Hereditary Deformity Appeared in Five Generations", *Brit. M. J.*, 1: 975–976.

HEDGEKATTI, R. M. 1939. "Congenital Malformations of Hands and Feet in Man", *J. Hered.*, 30: 191–196.

JOHNSTON, O. AND DAVIS, R. W. 1953. "On the Inheritance of Hand and Foot Anomalies in Six Families", *Am. J. Human Genet.*, 5: 356–372.

LEWIS, T. AND EMBLETON, D. 1908. "Split-hand and Split-foot Deformities and Their Types, Origin and Transmission", *Biometricka*, 6: 26–58.

MACKENZIE, H. J. AND PENROSE, L. S. 1951. "Two Pedigrees of Ectrodactyly", *Ann. Eugen.*, 16: 88–96.

PEARSON, K. 1931. "On the Existence of the Digital Deformity—So-called 'Lobster Claw' in the Apes", *Ann. Eugen.*, 4: 339–340.

POPONOE, P. 1937. "Split-hand", *J. Hered.*, 28: 174–176.

REED, T. E. AND FALLS, H. F. *In press.* "A Pedigree of Aniridia with a Discussion of 'Cluster Mutation' in Man", *Am. J. Human Genet.*

SCOTT, W. 1933. "Syndactylism with Variations", *J. Hered.*, 24: 241–243.

Genetic Study of Microcephaly Based on Japanese Material*

TAKU KOMAI, KEN'ICHI KISHIMOTO AND YASUNOSUKE OZAKI

National Institute of Genetics, Misima, Research Institute of Environmental Medicine, Nagoya University, and National Institute of Public Health, Tokyo

INTRODUCTION

MICROCEPHALY is one of the most severe congenital abnormalities found in man. Its main characteristics are a distinctly small skull and brain, extreme idiocy, underdeveloped body and some neuropathic symptoms. Although it is rare it may be found in both the Caucasian and Mongolian races and possibly in other races as well (Greenfield and Wolfsohn 1935). The cases occurring in the different races have many similar features. Great interest attaches to the genetic study of this abnormality, because of its severity, its conspicuousness and its rarity. Most of the microcephalics are undoubtedly of genetic origin, but there are cases apparently due to non-genetic causes. It is difficult to distinguish, at least superficially, the non-genetic from the genetic. The Japanese investigators of this problem seem to have an advantage over the European or American workers in that microcephaly of genetic origin is apparently more common among Japanese than among occidental peoples. This greater incidence is based upon these facts: (1) the higher rate of consanguinous marriages among the Japanese and (2) the almost total lack of pelvic irradiation in the pregnant mother.

Ozaki, one of the authors, started the study more than ten years ago, and published a part of his findings in 1940. His material came principally from the city of Tokyo and the Kanto and Hokuriku Districts. Kishimoto also collected material for several years, chiefly from Nagoya and its vicinity. Komai became interested in this problem in 1949, mainly as a result of coming across two microcephalic brothers residing in a village near Misima. His material was gathered mostly from districts between Tokyo and Misima. The authors have also incorporated data, both published and unpublished, obtained by other Japanese investigators, whenever such data were accompanied by sufficient and reliable information relative to patients and their parents and sibs. Thus we have been able to study a total of 143 cases belonging to 78 sibships. This datum is certainly fairly extensive for this rare abnormality, and it has enabled us to deduce some genetic conclusions from its study.

THE ETIOLOGY OF MICROCEPHALY

It now seems fairly well established that microcephaly may be due either to genetic or to non-genetic causes. As for the latter, Zappert (1927), Goldstein (1929), Goldstein and Murphy (1929), Murphy (1947) and Glass (1944) give evidence that x-ray pelvic irradiation during the early period of pregnancy may result in microcephaly in

Received January 24, 1954.
* Contribution No. 63 from National Institute of Genetics, Japan.

the child. More recently, Plummer (1952) published a highly remarkable finding to the effect that of the 11 four-and-a-half year old children whose mothers had been exposed during the first 20 weeks of gestation to the atomic bomb blast in Hiroshima within 1200 meters from the hypocenter, 7 were microcephalic. Some fetal diseases such as encephalitis (Hallervolden 1950), meningitis (Thelander and Goebel 1949), and the mother's infectious diseases, notably rubella, (Swan *et al.* 1943, Murphy 1947, Lande 1950) have been suspected of being responsible for the production of a microcephalic child. The suggestion has also been made that the unusual pressure of a gravid uterus on the fetus (Ernst 1908), or lack of space as in a case of a twin pregnancy (Verschuer 1945), may cause microcephaly. It seems to us, however, that the evidence for the production of microcephaly by non-genetic agents other than irradiation is not convincing. At any rate, such non-genetic microcephaly, even when the cases caused by irradiation are included, form but a small fraction of patients with this defect. This seems to be especially true of the present material where no case of maternal pelvic irradiation is included. The great majority of microcephalic cases is undoubtedly of genetic origin. This view is supported above all by (a), the high incidence of consanguinous matings among the parents of these abnormal children, and (b), the frequent occurrence of more than one case in the same kindred.

Relative to the development of microcephaly, Virchow's theory is often quoted. According to this, the premature synostosis of cranial sutures is the primary change which obstructs the further growth of the brain. This view, however, has been contradicted by most of the subsequent authors who maintain that the arrest of normal development of the brain precedes the premature synostosis of cranial sutures; or there is some fundamental cause which hinders the normal development and differentiation of both the brain and the cranium. The premature synostosis of cranial sutures is considered by many recent authors, such as Biemond (1938), Grebe (1939), Brenner (1951) and Böök *et al.* (1953) as the distinctive feature of a microcephalic skull.

C. Vogt suggested that microcephalics represent an atavistic type. Certainly, the small and "aviform" head, with an "Aztec-type" slanting brow, flattened occiput, relatively large and protruding facial region, receding lower jaw, together with the small stature, curved spine, stooping posture, flexed knees and apparently long extremities, simulate an ape type. The mentality, which in many cases hardly surpasses that of a one-year old child, and the manner of walking and hopping enhance this similarity. Naturally, microcephalics are called "ape-men" both in the western countries and in Japan. Some Japanese country people say that this type of abnormal child is born in the family of a hunter as a curse on him for having killed pregnant monkeys.

The atavistic theory of Vogt has been disputed by many subsequent authors who consider that the features of the microcephalic idiots enumerated above are due to the impairment of normal development plus pathological changes. As a matter of fact, severe anomalies in macroscopic and microscopic structures of the brain have been demonstrated by several authors at autopsy of the brains of microcephalics (Ernst 1908, Stringaris 1929, Mayer and Reisch 1930, Greenfield and Wolfsohn 1935).

No less extraordinary than the atavistic theory is Jelgersma's opinion (1928) that microcephalics represent a phylogenetically more *advanced* type than normal individuals, because their physique shows less "fetalization". This opinion, as well as the atavistic theory, ignores the pronounced pathological features in the structure and function of the body of microcephalics, and hardly merits more than historical interest.

The majority of microcephalics may be characterized as low grade idiots. Many can not speak a single word, others have a very scanty baby-type vocabulary. Some require feeding and toilet care throughout life. Most are apparently lacking in ordinary feeling and emotion. They usually look happy and cheerful, though often irritable. Interest in the opposite sex is lacking except in the case of a few male microcephalics of relatively high grade. Epileptic and convulsive disorders are common, and evidence of hypofunction of the pyramidal system is almost always present. (For further clinical characteristics of microcephaly, see Mayer and Reisch 1930, Kürbitz 1931, Dubitscher 1937 and Tredgold 1949).

Many authors follow Giacomino's classification of microcephaly into microcephalia vera, microcephalia spuria and microcephalia combinata. Microcephalia vera includes the microcephalics characterized by the small brain without any trace of injury or deformation, while spuria includes those in which there is some trace of injury or pathological change, and combinata includes those which combine the smallness of the brain with a trace of injury. This rather arbitrary distinction can not be of any fundamental significance, especially since there are apparently cases where the injury has been completely repaired.

Böök *et al.* (1953) suggest that the term microcephaly should be used only for descriptive purpose when "the skull is smaller than the average in the respective population at the respective age, minus three times the standard deviation, and when the defect is not caused by the premature synostosis of the cranial sutures" (p. 638). Such a definition of microcephaly is difficult to adhere to in all studies, because it requires autopsy for the diagnosis of each case. We feel justified in taking the small size of the skull as the most important criterion for diagnosing microcephaly, but at the same time taking into consideration the Aztec-type head form, as well as other features commonly occurring in this type of abnormality.

THE MATERIAL

The material for the present study consists of 143 cases (93 males and 50 females) belonging to 78 sibships obtained from all parts of Japan. We examined most of the patients either independently or conjointly. Necessary physical and psychiatric examinations were carried out for each case whenever possible. Care was taken to exclude idiots who were not microcephalic, even when measurements were not feasible. Although the strict criteria recommended by Böök *et al.* were not followed in the diagnosis of each case, the figures for head circumference of the cases presented in table 1 give assurance that no case of other type is included in our material. Rather, there is danger that some border-line cases were missed. Some cases drawn from the

TABLE 1. THE MATERIAL OF MICROCEPHALICS USED FOR THE PRESENT STUDY

Sibship No.	Size and Composition of Sibship	Number of Microcephalics	Sex, Age and Head Circumference (cm)
1a	**3**(f m m)	**3**	f 10 (40.0), m, m 7 (38.0)
1b	**2** (F m)	**1**	m 11 (36.0)
1c	4 (m F f F)	2	m 17 (39.0), f 13 (42.0)
1d	4 (m F m F)	2	m 8 (40.0), m 2 (36.0)
2	**6** (M F f M f m)	**3**	f 17 (41.5), f 11 (38.0), m 8 (37.0)
3	10 (F M M F M m F M m M)	2	m 30 (41.0), m 23 (41.0)
4	6 (M F M f F f)	2	f, f 35
5a	7 (F M M m F F F)	1	m 66 (41.0)
5b	7 (F m F F F [F M])	1	m 23
6	**5** (m F M F M)	**1**	m 33
7	**7** (F m M F F M F)	**1**	m 15 (37.8)
8	5 (m M F F m)	2	m 19 (47.0), m
9	3 (m M M)	1	m 11 (46.0)
10a	5 (M M f M M)	1	f 39 (43.0)
10b	**7** (M f F M M F F)	**1**	f 12 (40.0)
10c	**8** (F F M M m M M F)	**1**	m 43 (47.0)
10d	**4** (m m F F)	**2**	m 20 (45.0), m 10 (44.0)
10e	**3** (m f M)	**2**	m, f
10f	3 (F F m)	1	m
10g	**4** (M M M f)	**1**	f
10h	4 (m F M F)	1	m
11	**3** (m f m)	**3**	m, f, m 10 (46.0)
12	6 (F M F f m M)	2	f 22, m 21 (42.0)
13	6 (f F M M M M)	1	f 21
14	**8** (F M F m f m M M)	**3**	m 12, f, 8, m 7
15	5 (M f F F m)	2	f 22 (42.0), m 13 (42.0)
16	6 (M F M F F m)	1	m 13
17	4 (m F M F)	1	m 10 (39.0)
18	2 (M f)	1	f 11 (35.0)
19	3 (f f f)	3	f, f, f
20	**4** (f M f M)	**2**	f 13 (38.0), f 5 (38.5)
21	4 (m F F F)	1	m 13 (43.0)
22	**5** (M M m M F)	**1**	m 23
23	7 (m F F M m M M)	2	m 23, m (49.0)
24	5 (F M m F M)	1	m 28 (41.0)
25	4 (m M F F)	1	m 15 (44.0)
26	3 (m F M)	1	m 7 (46.0)
27	7 (F m M F m M F)	2	m 21, m 15 (47.0)
29	**6** (M f F M f M)	**2**	f 27, f 18
30	**6** (F m F M M F)	**1**	m 31 (47.0)
31	2 (M m)	1	m 3
32	**5** (m M m F m)	**3**	m, m, m
33	**7** (m[F F]F m F f)	3	m, m 6 (36.0), f 2 (33.0)
***34**	**3** (m M F)	**1**	m 22
***35**	**4** (M m m m)	**3**	m 8, m 6, m 4
***36**	**10** (m m m F M f F m F F)	**5**	m 22 (504), m 20 (692), m, f, m 15 (544)**
***37**	**12** (M m M f M M F f f F F M)	**4**	m, f, f 18 (31.0), f 16 (37.2)
*38a	6 (m f f F F m)	4	m, f, f, m 34

TABLE 1. *Continued*

Sibship No.	Size and Composition of Sibship	Number of Microcephalics	Sex, Age and Head Circumference (cm)
*38b	4 (f U U U)	1	f 22
39	**7** (m M m m M f f)	**5**	m, m, m 41 (44.0), f, f
***40**	**5** (m f M F F)	**2**	m, 19, f 17
***41**	**5** (m M m m M)	**3**	m, m 31, m 25 (39.0)
***42**	**5** (F M M m m)	**2**	m 11 (41.0), m 9 (41.0)
*43	6 (m m f M m m)	5	m 17, m, f 14, m 9, m 7
*44	2 (m F)	1	m 18
45	5 (f F M M F)	1	f 17
***46**	**4** (M m M F)	**1**	m 40
47	6 (M F M F[F f])	1	f 1.5 (31.5)
48	4 (m m f M)	3	m, m, f
50	5 (m M f M m)	3	m 25 (45.0), f 18 (45.3), m 11 (42.8)
51	**5** (F F F M m)	**1**	m 8 (40.5)
52	6 (F M M F m m)	2	m 12 (46.0), m 10 (44.5)
53	2 (M f)	1	f 6 (38.8)
54	8 (M M f F F M M M)	1	f 27 (48.0)
55	**10** (M M M M F M M F F m)	**1**	m 16
56	10 (F M F M M F M M F m)	1	m 15 (46.5)
57	6 (m M F M f F)	2	m 10 (45.0), f
58	2 (m M)	1	m 10 (47.0)
59	5 (F F M f f)	2	f 9 (44.5), f 7 (40.3)
60	3 (F F m)	1	m 13 (41.7)
61	7 (F[f f]M F M f)	3	f 13 (42.6), f 13 (44.0), f 2 (36.0)
62	8 (F F m f M m F F)	3	m 35 (49.5), f 33 (45.0), m 27 (46.5)
63	4 (F F m M)	1	m 11 (46.0)
64	1 (m)	1	m 13 (45.0)
65	8 (M F M M M M M m)	1	m 9 (42.0)
66	3 (f f m)	3	f 7 (35.0), f 5 (34.0), m 2 (33.5)
67	6 (F M M M F m)	1	m 3 (34.7)
68	**7** (m M m M M M F)	**2**	m, m
Total....	409	143	

Progeny of first-cousin marriage are shown by bold type; different sibships sharing the same numeral belong to the same kindred.

* Cases which were not examined by the authors.

U Healthy child whose sex is unrecorded.

□ Twins.

** Calculated cranial capacity.

literature or from personal communication and judged sufficiently authentic are also included. These are as follows:

Sibship No.	*Authority*	*Literature*
34	Sako, M.	Iden 2: 150–151
35	Sako, M.	Iden 2: 150–151
36	Yanasé, T. & Y. Nisihara	(Personal communication)
37	Matusita, K.	(Personal communication)
38	Takeda, H.	Man and Heredity 1: 119–121
	Hattori, S.	(Personal communication)

Sibship No.	*Authority*	*Literature*
40	Tanabé, K.	(Personal communication)
41	Watanabé, T.	Mitt. Med. Fak. K. Univ. Tokyo 28: 77–124
	Hara, T.	Folia Anat. Jap. 5: 1–8
42	Yosida, T.	Osaka Igaku 42: 1460–1461
43	Miyao, G., E. Sasaki, R. Minamino	Man and Heredity 2: 65
44	Kaji, S.	(Personal communication)
46	Hattori, S.	(Personal communication)

There is one possible source of error in regard to the present material, namely, the inaccuracy of data pertaining to dead individuals. We hope we have minimized its possible effect by carefully checking all information and also by making our material extensive.

GENETIC ANALYSIS OF THE MATERIAL

All the microcephalic patients in our collection are the progeny of apparently normal parents. Moreover, no case suspected of non-genetic origin seems to be included. These facts suggest that they are due to an autosomal recessive gene. The

TABLE 2. THE MATERIAL ARRANGED ACCORDING TO THE SIZE OF SIBSHIP (s) AND THE NUMBER OF ABNORMALS CONTAINED IN EACH SIBSHIP (r) n_s—NUMBER OF SIBSHIPS, r_s—NUMBER OF ABNORMALS, l_s—NUMBER OF SIBS

s	r					n_s	r_s	l_s
	1	2	3	4	5			
2	6	—	—	—	—	6	6	12
3	5	1	4	—	—	10	19	30
4	8	4	2	—	—	14	22	56
5	6	5	3	—	—	14	25	70
6	5	5	1	1	1	13	27	78
7	4	3	2	—	1	10	21	70
8	3	—	2	—	—	5	9	40
10	2	1	—	—	1	4	9	40
12	—	—	—	1	—	1	4	12
Total.....	39	19	14	2	3	77 (N)	142 (R)	408 (T)

material has been analyzed according to this presumption. Since the method of selection of the data was "arbitrary" (Haldane 1938), or of "incomplete multiple selection" (Bailey 1951), the analysis was carried out following Haldane (1938). From the material arranged in table 2, the frequency of the recessives (p) was found first by Weinberg's sib-method:

$$p = \frac{\sum_{r=1}^{s} r(r-1) \sum_{s=2}^{8} a_{rs}}{\sum_{s=2}^{8} (s-1) r_s}$$

where a_{rs} is the recorded number of sibships consisting of s members, r of whom are abnormal. Thus, .3126 was obtained as the first approximation to the real value of p. This value was substituted on the right-handed side of the equation:

$$\frac{R}{p} = \sum_{s=2}^{S} \frac{l_s}{1 - q^s}$$

and a better value .2959 was obtained for p. The same procedure was repeated, and at the seventh iteration, we arrived at .2855 which was fixed for all the four figures. This value was taken as p, and its standard error was found by the formula:

$$\sigma_p^{-2} = \frac{R}{p^2 q} - \frac{1}{q^2} \sum_{s=2}^{S} \frac{s q^s l_s}{(1 - q^s)^2}$$

The value .0265 was obtained for σ_p. The difference between .2855 and .25, (.0355) is smaller than twice the standard error, namely, $2\sigma_p = .053$.

The value for p_0 was next found on the assumption of $k = 0$, that is, the assumption that our data included the abnormals in the same proportion as in the general population. The value for p_0 was obtained by means of the formula:

$$p_0 = \frac{R - N}{T - N}.$$

Here $R = 142$, $N = 77$, $T = 408$, so $p_0 = .1964$. The standard error for this value was found by:

$$\sigma_{p_0}^{-2} = \frac{T - N}{pq}.$$

The σ_{p_0} thus obtained is .0218, and the difference between .25 and p_0 (.25 − .1964 = .0536) is 1.23 times $2\sigma_{p_0}$. Still, we seem to be justified to conclude that the data of microcephaly in our collection are consistent with the presumption that this abnormality is due to an autosomal recessive gene.

OTHER GENETIC OR NON-GENETIC FACTORS AS POSSIBLE CAUSES OF MICROCEPHALY

1. Sex

Attention may be called to the sex-ratio in our microcephalic material. It includes 93 males and 50 females. This deviation from equality is statistically significant, and agrees with Bernstein's statement (1922), that the anomaly occurs about twice as often among males as among females. Among the 1280 cases of mental defect under the care of the Royal Eastern Counties' Institution studied by Penrose (1938*a*) there were 22 microcephalics of whom 18 were males. If this preponderance of males among microcephalics is universal, one must seek the reason for it.

Haldane (1938), as well as Hogben (1931), has called attention to the equally significant preponderance of males among the albinos. He attributes this to the social cause that male albinos are more likely than female albinos to be met outside their

TABLE 3. THE MATERIAL ARRANGED ACCORDING TO THE NUMBER OF ABNORMALS AND THEIR SEXES

Number of Abns. in Each Sibship	Number of Sibships	Number of Abnormals		Percentage of Males	Probands		Secondary Cases	
		m	f		m	f	m	f
1	1m—29 1f—10	29	10	74.4	—	—	—	—
2	2m—9 1mlf—6 2f—4	24	14	63.2	14.1	4.9	9.9	9.1
3	3m—3 2mlf—7 1m2f—2 3f—2	25	17	59.5	10.4	3.6	14.6	13.4
4	2m2f—1 1m3f—1	3	5	37.5	1.5	.5	1.5	4.5
5	4mlf—2 3m2f—1	11	4	73.3	2.2	.8	8.8	3.2
Total.....		92	50		28.2	9.8	34.8	30.2

residences, and the probands, or the members with whom the investigation of a sibship begins, will more often be males than females. To test this hypothesis, he arranged the material available to him according to the number of albinos included in each sibship. The probands in the sibships including two or more albinos were supposed to be of the same sex-ratio as in the sibships including a single albino. When the numbers of these probands were subtracted from the numbers of the members in each group, the remaining secondary cases should be of the normal sex-ratio if the above hypothesis is valid. Actually he found that this was the case with his material.

Our material of microcephalics as arranged in table 3 has been examined in the same way. It may be noticed that the sex-ratio tended to decrease with the number of abnormals in the sibship. The probands were divided into sexual groups in the same ratio as in the sibships including a single patient, namely, 74.4:26.6. The sex-ratio in the secondary cases, 34.8:30.2, was close to the normal ratio. This finding seemed to show that the apparent preponderance of males among the microcephalics was merely due to the social cause as suspected by Haldane for albinos. However, question still remains as to whether this is the only cause of this remarkable tendency. Incidentally, it is to be noted that microcephaly is in contrast to anencephaly where the sexual disparity is significantly in favor of the female (Penrose 1946, Böök and Rayner 1949).

2. Birth order

The possible effect of birth order on the production of microcephalic children was examined by the method used by Penrose (1946) for the same problem relative to anencephaly, spina bifida and congenital hydrocephaly. The ratio of abnormals to total sibs was assigned to each sib, either normal or abnormal. This value gave the probability of each sib being affected if there were no effect of birth order. The total

TABLE 4. EXAMINATION OF POSSIBLE EFFECT OF BIRTH ORDER ON THE PRODUCTION OF MICROCEPHALIC CHILD

Birth Order	Number of Microcephalic Children	
	Observed	Calculated
1	35	29.480
2	27	28.647
3	24	25.130
4	12	19.387
5	19	15.794
6	13	11.097
7	5	6.718
8	4	3.658
9	2	1.233
10	2	1.233
11	0	.333
12	0	.333
Total	143	143.043
Mean	3.406	3.165 ± 1.86 (S.D.)
Difference	3.406 − 3.165 = .241 ± 1.56 (S.E.)	

value for each birth order was compared to the actual number of abnormals found among the members of the corresponding order. The data thus obtained are presented in table 4. The observed mean of birth order was 3.406, while the calculated mean was 3.165 ± 1.860 (S.D). The difference 3.406 − 3.165 = .241 ± .156 (S.E.) is not significant. The 51 cases collected from literature were examined similarly. The observed mean of birth order was 4.04, while the calculated mean was 4.08 ± 2.54 (S.D.). The difference 4.08 − 4.04 = .04 ± .36 (S.E.) is again short of being significant. Thus, it seems safe to state that there is no effect of birth order on the production of microcephalic children.

3. Maternal age

We have data on the maternal age for only 91 microcephalics in our material. Relative to these the possible effect of maternal age on the production of microcephalic children was examined. The data for the distribution of the maternal age in the births which occurred in the year 1943 in the whole Japanese population published by the government were taken as the standard. For the sake of simplicity, the numbers of births for each age group were assembled into classes with 5-year intervals. The actual numbers thus obtained were converted into percentage values. The same procedure was followed for mothers of microcephalics. As shown in table 5, the microcephalic group showed a distribution similar to the general group in the relative incidence of births according to age. The mean maternal age was calculated from the data, by taking the median value of each class as the representative value of the class. The results showed that the mean maternal age of the whole population was 29.706, while that of the microcephalic group was 29.654. Although the pro-

TABLE 5. EXAMINATION OF POSSIBLE EFFECT OF MATERNAL AGE ON THE PRODUCTION OF MICROCEPHALIC CHILD

Age of Mother	Japanese General Population		Mothers of Microcephalics	
	Number of births	Ratio	Number of births	Ratio
Up to 15	226	.01	—	—
16–20	80,977	3.72	8	8.79
21–25	524,864	24.12	18	19.80
26–30	648,597	29.80	24	26.37
31–35	523,359	24.05	24	26.37
36–40	296,061	13.60	11	12.09
41–45	93,611	4.30	6	6.60
46–50	6,808	.31	—	—
51 and up	1,778	.08	—	—
Total	2,176,281	99.99	91	100.02
Mean age	29.706 ± 6.15 (S.D.)		29.654 ± 6.70 (S.D.)	

cedure was a rough approximation, the two comparable values were so close together, that we feel warranted in saying that there is no significant relation between the maternal age and the incidence of microcephaly. This finding is in contrast to what has been found by Penrose (1946) for anencephaly, spina bifida and congenital hydrocephaly where "advancing maternal age is significantly related to the incidence of this group of malformations." (p. 78). Polman (1950), however, could not confirm this finding in the material of the same sorts of congenital malformations examined by him.

MENTAL RETARDATION AMONG RELATIVES

In our pedigrees several mentally retarded individuals occurred among the relatives of the microcephalics. Since the records were made rather casually, it was difficult to make any reliable estimate of the incidence of such individuals. It was fairly certain, however, that the incidence was considerably higher among the relatives of the microcephalics than within the general population. Penrose (1938*a*) found in his material higher incidence of psychopathy among relatives of microcephalics than in the general population. The mentally retarded relative in our pedigrees was a parent, grandparent, sib, first cousin or a more remote relation. It was not clear in many cases whether the mentally retarded individuals were heterozygous for the gene responsible for microcephaly, except in cases where they were parents of the patient. Böök *et al.* 1953) found indications that heterozygotes might be slightly abnormal. The great majority of the heterozygotes were of normal physique and mentality, as far as could be judged by interviews we had with the parents of microcephalics. This seems to assure the validity of the calculations of the incidence and mutation rate of the gene which are presented in the next section and which are based on the recognition of complete recessivity of the gene responsible for microcephaly.

ESTIMATION OF THE INCIDENCE OF THE GENE FOR MICROCEPHALY

Dahlberg's formula (1947, 1948) has been followed for this purpose:

$$q = \frac{c(1 - k)}{16k - 15c - ck},$$

where q is the incidence, k the proportion of the microcephalics who are the progeny of first-cousin matings among the whole microcephalic population, and c is the proportion of first-cousin matings among the population in general. In the present material k is .448. The exact figure for c in the Japanese population is unknown. According to the recent data obtained by the Atomic Bomb Casualty Commission (ABCC) for the populations in Hiroshima, Kure and Nagasaki, c is .04. This figure is too low to be taken here, as it is from the cities mentioned above and is a very recent one. Under the assumption of $c = .04$, we obtain $q = .0034$; if $c = .05$, $q = .0043$; if $c = .06$, $q = .0053$, and if $c = .07$, $q = .0063$. Böök *et al.* (1953) estimated the incidence of the gene for microcephaly in the Swedish population on a different basis. They found that the value is probably between 1/230 and 1/162 which corresponds respectively to .0043 and .0062. There is thus a good agreement between their estimation and ours. It is to be noted also that these figures are close to the figures for the incidence of the genes of equally rare congenital abnormalities thus far found, such as albinism, congenital amaurotic idiocy of the infantile type, total color blindness and hemophilia (Neel *et al.* 1949, Neel and Falls 1951, Neel 1952).

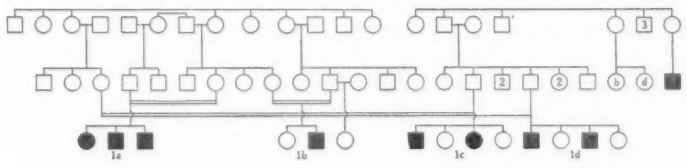


FIG. 1

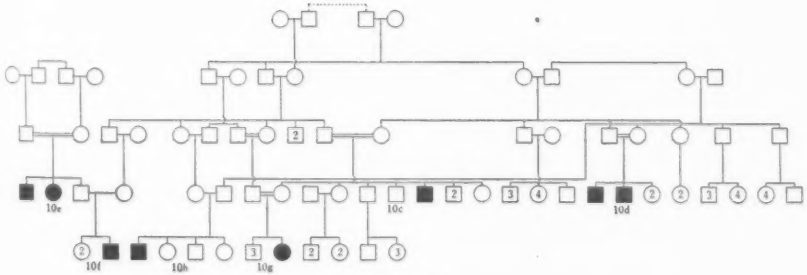


FIG. 2

FIGS. 1 and 2. Two large pedigrees containing many microcephalics in the authors' collection. First-cousin couples are connected by double horizontal lines.

FIG. 1: the main part of kindred no. 1 (Sibship no. 1a–1d); b—blind, d—dumb.

FIG. 2: the main part of kindred no. 10 (Sibship no. 10c–10g).

It is very likely that there is unevenness in the distribution of the gene for microcephaly within the Japanese population, such as was found by Dahlberg (1948) and Dunn (1947) primarily for the gene for the infantile type of amaurotic idiocy within the Swedish population. For instance, both the districts around Yokosuka which is the home of kindreds No. 1 (fig. 1), No. 4 and No. 50, and also the village Sakai in Toyama Prefecture where the large kindred No. 10 (fig. 2) has been located, are undoubtedly the localities where the incidence is higher than elsewhere.

RATE OF MUTATION OF THE GENE FOR MICROCEPHALY

The rate of mutation of the gene for microcephaly has been estimated on the assumption of a state of equilibrium of the gene in the population. The formula employed is:

$$m = (1 - f)\,[\alpha q + (1 - \alpha)q^2] \qquad \text{(Li 1948, Neel } et\ al. \text{ 1949, Neel 1952)}$$

where m stands for the mutation rate, f the relative fertility of the patients, q the gene frequency, and α the mean coefficient of inbreeding. In general, the fertility of microcephalics is almost zero. However, five of them within our material had children, so we have put $f = .02$. Hence, if $c = .04$ and $\alpha = .0032$ (ABCC data) and $q = .0034$, then $m = 2.20 \times 10^{-5}$. If $c = .05$, $\alpha = .004$, and $q = .0043$, m becomes 3.49×10^{-5}; If $c = .06$, $\alpha = .005$, and $q = .0053$, m becomes 5.34×10^{-5}; If $c = .07$, $\alpha = .006$, and $q = .0063$, m becomes 7.57×10^{-5}.

In view of the more or less arbitrary nature of the values assumed for c, α and f, the values obtained for q and m must not be considered very accurate. It is to be noted, however, that the values here obtained for q and m resemble the corresponding figures for the genes responsible for the several kinds of rare congenital abnormalities, mentioned already, which occur in man. (Neel *et al.* 1949, Neel and Falls 1951, Neel 1952).

SUMMARY

1. 143 (93 male and 50 female) cases of microcephaly belonging to 78 sibships have been found within the Japanese population. This number includes 32 cases belonging to 12 sibships reported by other Japanese investigators. The proportion of the microcephalics who are the progeny of first-cousin matings among the present material is 44.8 per cent.

2. Analysis of the material according to Haldane's method (1938), indicates that microcephaly is due to a recessive autosomal gene. The recessivity is complete in the majority of cases. Apparently in a few instances the heterozygote manifests a slight effect of the gene.

3. A significantly higher percentage of males than females was found among the microcephalics. This sexual disparity seems to be a universal phenomenon. This is apparently due in a large measure to the fact that the male microcephalics are generally more frequently met outside their homes, and they are more likely to become the probands of the pedigrees.

4. Neither birth order nor mother's age seems to affect the relative incidence of microcephaly. Secondary factors, if any, whether genetic or non-genetic, which are

responsible for the production of the abnormality, and which might affect either the fetus or mother, are apparently unimportant, at least so far as the present material is concerned.

5. The incidence of the gene for microcephaly calculated by Dahlberg's formula is .0034–.0063, if .04–.07 is accepted as the proportion of first-cousin matings in the general population. This value for the incidence of the gene obtained for the Japanese population coincides closely with .0043–.0062, the corresponding value obtained for the Swedish population by Böök *et al.*

6. The rate of mutation of the gene for microcephaly has been estimated on the assumption of an equilibrium state of the incidence of the gene in the population. The value $(2.20–7.57) \times 10^{-5}$ has been obtained, depending on the values chosen for, c, the proportion of first cousin matings in the general population, α, the mean coefficient of inbreeding, and q, the incidence of the gene. The value comes close to the mutation rates estimated by other authors for certain other rare congenital diseases of man.

ACKNOWLEDGMENTS

In collecting the material of the study, we were aided by a number of fellow scientists and personal friends whose names are too numerous to mention here, but whose assistance is appreciated. The cooperation of the relatives and neighbors of the patients, as well as of the officials in registration bureaus is also acknowledged. In our search of the literature, we were aided by Drs. D. J. McDonald, J. Warkany, L. S. Penrose, W. Brenner, G. Plummer, J. A. Böök, Y. Handa, H. Maki and Mr. N. Fujiki, and are indebted to them. We owe valuable criticism and suggestion to Dr. D. J. McDonald, Dr. H. H. Strandskov and the co-editors of this journal. The expense of the study was defrayed in part by a grant from the Japanese Ministry of Education. We record here our deep appreciation of this aid.

REFERENCES

Allan, W., Herndon, C. N. and Dedley, F. C. 1944. Some examples of the inheritance of mental deficiency; apparently sex-linked idiocy and microcephaly. *Am. J. Mental Deficiency* 48: 325–334.

Bailey, T. J. 1951. A classification of methods of ascertainment and analysis estimating the frequencies of recessives in man. *Ann. Eugenics* 16: 223–225.

Benda, C. E. 1941. Microcephaly. *Am. J. Psychiat.* 97: 1135–1146.

Bernstein, C. 1922. Microcephalic people sometimes called "pin-heads". *J. Heredity* 13: 30–39.

Beswick, R. C., Warner, R. and Warkany, J. 1949. Congenital anomalies following maternal rubella. *Am. J. Diseases Children* 78: 334–348.

Biemond, A. 1938. *Ann. anat. pathol. et anat. norm. méd. chir.* 15: 883. (Cited from Brenner, W., 1951.)

Böök, J. A. and Rayner, S. 1949. A clinical and genetical study of anencephaly. *Am. J. Human Genet.* 1: 61–84.

Böök, J. A., Schut, J. W. and Reed, S. C. 1953. A clinical and genetical study of microcephaly. *Am. J. Mental Deficiency* 57: 637–660.

Brenner, W. 1951. Zur Frage der Erblichkeit von Mikrocephalie und Hydrocephalie. *Z. Menschl. Vererbungs u. Konstitutionslehre* 30: 375–402.

Brügger, C. 1939. Die Vererbung des Schwachsinns. Handbuch der Erbbiologie des Menschen 2: 750–751.

Dahlberg, G. 1947. Mathematical Methods for Population Genetics. Basel a. New York.

Dahlberg, G. 1948. Genetics of human populations. *Advances in Genet.* 2: 69–98.

Dubitscher, F. 1937. Mikrenzephalie. "Handbuch der Erbkrankheiten". 1. Schwachsinn: 106–110.

DUNN, L. C. 1947. The effect of isolates on the frequency of a rare human gene. *Proc. Nat. Acad. Sci. U. S.* 33: 359–363.

ERNST, F. 1907–1908. Mikrocephalie, Mikrencephalie. Schwalbe's "Die Morphologie der Missbildungen des Menschen und der Tiere". 2. Abth. Missbildungen der einzelnen Organe und Organsysteme: 190–214.

GLASS, S. J. 1944. Dwarfism associated with microcephalic idiocy and renal rickets. *J. Clin. Endocrinol.* 4: 47–53.

GOLDSTEIN, L. 1929. Radiogenic microcephaly. *Arch. Neurol. Psychiat.* 27: 102–115.

GOLDSTEIN, L. AND MURPHY, D. P. 1929. Etiology of the ill-health in children born after maternal pelvic irradiation. Pt. II. Defective children born after post-conception pelvic irradiation. *Am. J. Roentgenol.* 22: 322–331.

GREBE, H. 1939. Beitrag zur familiären Mikcrocephalie. *Z. menschl. Vererbungs-u. Konstitutionslehre* 24: 506–515.

GREENFIELD, J. G. AND WOLFSOHN, J. M. 1935. Microcephalia vera. A study of two brains illustrating the agyric form and the complex microgyric form. *Arch. Neurol. Psychiat.* 34: 1296–1316.

HALDANE, J. B. S. 1938. The estimation of the frequencies of recessive conditions in man. *Ann. Eugenics* 8: 255–262.

HALLERVOLDEN, J. 1950. Ueber diffuse symmetrische Kalkablagerungen bei einem Krankheitsbild mit Mikrocephalie und Meningocephalitis. *Arch. Psychiat. Nervenkrankh.* 184: 579–600.

HALPERIN, S. L. 1944. Three pedigrees of microcephaly, with a note on their genetic implications. *J. Heredity* 35: 211–214.

HARA, A. 1940. Three cases of microcephaly, with special reference to the abnormality in visceral organs. (in Japanese) *Keio Igaku* 20: 150.

HOGBEN, L. 1931. The genetic analysis of family traits. *J. Genet.* 25: 97–112.

JELGERSMA, H. C. 1928. Die sogennante Entartungszeichen der Mikrocephalen und die Fetalisationslehre. *Zeit. Neur. u. Psychiat.* 112b: 88–100.

KOMAI, T., KISHIMOTO, K. AND OZAKI, Y. 1953. Genetic studies of human microcephaly (Preliminary report). *Proc. Japan Acad.* 29: 220–223.

KÜRBITZ, W. 1931. Mikrocephalie und Schwachsinn. *Arch. Psychiat. Nervenkrankh.* 90: 172–197.

LANDE, L. 1950. Congenital malformation with severe damage to the central nervous system due to early fetal virus infection. *J. Pediat.* 36: 625–634.

LI, C. C. 1948. An Introduction to Population Genetics. Peiping.

MAYER, C. AND REISCH, O. 1930. Klinische Studien an zwei Mikrocephalen. *Arch. Psychiat. Nervenkrankh.* 89: 662–689.

MITSUKAWA, M. 1937. Clinical observation on a microcephalic idiot with nanosomia. (in Japanese). Papers Comm. 15th Anniv. Dept. Neur. Keio Univ.: 122–159.

MIYAO, G., SASAKI, E. AND MINAMINO, R. 1949. A pedigree of microcephaly. (in Jap.). *Man and Heredity* 2: 65.

MURPHY, D. P. 1947. Congenital Malformations. 2nd ed., Philadelphia.

NEEL, J. V. 1952. The study of human mutation rates. *Am. Naturalist* 86: 129–144.

NEEL, J. V. AND FALLS, H. F. 1951. The rate of mutation of the gene responsible for retinoblastoma in man. *Science* 114: 419–422.

NEEL, J. V., KODANI, M., BREWER, R. AND ANDERSON, R. C. 1949. The incidence of consanguineous matings in Japan, with remarks on the estimation of comparative gene frequencies and the expected rate of appearance of induced recessive mutations. *Am. J. Human Genet.* 1: 156–178.

OZAKI, Y. 1940. The inheritance of microcephaly. (in Japanese). *Minzoku-eisei* 8: 159–168.

PATERSON, D. 1926. Case of familial microcephaly. *Proc. Roy. Soc. Med. 19, Sec. Disease of Children:* 60.

PENROSE, L. S. 1938*a*. A clinical and genetic study of 1280 cases of mental defect. *Med. Research Council (Brit.); Spec. Rep. Ser. No. 229.*

PENROSE, L. S. 1938*b*. Some genetical problems in mental deficiency. *J. Mental Sci.* 84: 1–15.

PENROSE, L. S. 1939. Maternal age, order of birth and developmental abnormalities. *J. Mental Sci.* 85: 1–10.

PENROSE, L. S. 1946. Familial data on 144 cases of anencephaly, spina bifida and congenital hydrocephaly. *Ann. Eugenics* 13: 73–98.

PLUMMER, G. 1952. Anomalies occurring in children exposed in *utero* to the atomic bomb in Hiroshima. *Pediatrics* 10: 687–693.

POLMAN, A. 1950. Anencephaly, spina bifida and hydrocephaly. *Genetica* 25: 29–78.

SAKO, M. 1948. Two pedigrees of microcephaly. (in Japanese). *Idengaku-Zasshi* 2: 150–151.

SPENCER, W. G. 1920. Microcephaly in two sisters, children of first cousins, exhibited shortly after craniotomy. *Proc. Roy. Soc. Med. 13, Clin. Sec.*: 76–78.

STRINGARIS, M. G. 1929. Mikrencephalie. Ein Beitrag zur Lehre und Kasuistik der Missbildung. *Frankfurter Zeitschrift für Pathologie* 37: 396–467.

SWAN, C., TOSTEVIN, A. L., MOORE, B., MAYO, H. AND BLACK, G. H. B. 1943. Congenital defects in infants following infectious diseases during pregnancy, etc. (cited in Beswick, R. C., Warner, R. and Warkany, J. 1949).

THELANDER, H. E. AND GOEBEL, G. 1949. Microcephaly as a complication of pneumococcic meningitis. *Am. J. Diseases Children* 77: 642–646.

TREDGOLD, A. F. 1949. A Text-book of Mental Deficiency. 7 ed., London.

VERSCHUER, O. v. 1945. Erbpathologie. Dresden. (cited in Brenner 1951).

WATANABE, T. 1922. Ueber einen Fall von Mikrocephalie. *Mitt. Med. Fak. K. Univ. Tokyo* 28: 77–124.

YOSIDA, T. 1943. On the inheritance of microcephaly (A preliminary report). (in Jap.). *Osaka Igaku* 42: 1460–1461.

Zappert, J. 1927. Ueber röntgenoge fötale Mikrozephalie. *Arch. Kinderheilk.* 80: 34–50.

Intra-Uterine Selection by the ABO Incompatibility of Mother and Foetus[1]

EI MATSUNAGA

Department of Legal Medicine, Sapporo University of Medicine, Sapporo, Japan

INTRODUCTION

RECENT discoveries in regard to the interaction of certain inherited blood differences between mother and foetus have given a new realization of the dangers of isoimmunization of the mother by dominant factors in the foetal blood. The Rh blood factor has been shown to be responsible for the pathogenesis of a specific disease of the newborn, erythroblastosis fetalis, and thereafter some cases have been reported pointing out that the same disease could be caused also by the ABO incompatibility of mother and foetus. In connection with isoimmunization the term incompatibility is applied to those instances, when the mother is lacking the dominant blood factor, which is present in the foetus. Therefore, with respect to ABO blood groups the following instances are incompatible; mother O and foetus A or B, mother A and foetus B or AB, and Mother B and foetus A or AB. The matings which could produce the incompatiblity are defined as incompatible in contrast to those compatible matings in which the blood factors of the father and of the mother are identical or in which the mother carries the dominant blood factor (Table 1).

In this paper the author wishes to show with our Japanese materials the selective effect caused by the ABO incompatibility upon the population.

EVIDENCE OF SELECTION BY THE ABO INCOMPATIBILITY OF MOTHER AND FOETUS

There is some evidence of a shortage of children of certain blood groups from certain types of ABO matings. Hirzsfeld and Zborowski (1926) and later Levine (1943), in a study of the literature, observed that the incidence of A children was lower in the mating mother O x father A than in the mating mother A x father O. Waterhouse and Hogben (1947) have found that the observed deficiency of A children from the mating mother O x father A is very highly significant. These studies are indicating the possibility of selection by maternal foetal incompatibility.

Very recently the author (1953) has collected the results of thirteen family investigations from the literatures, issued from the department of legal medicine, both of Kanazawa Medical University (1914–1939) and Medical Faculty of Tokyo University (1939–1952). All the researches had been done under the instruction of Prof. T. Furuhata, and the materials consisted of 2,709 families with 6,360 children. Attention was focused on the O x A and O x B matings.

The results are summarized in Table 2 and compared with the expected number[2]

Received July 6, 1954.

[1] Presented at the World Population Conference, Rome, 1954.

[2] In order to calculate the expected number the results of gene frequency calculations in Japanese obtained by T. Kobayashi (1940) were used, i.e., p = 0.2774, q = 0.1707, r = 0.5519.

TABLE 1. BLOOD GROUP MATING

Compatible	Incompatible
Mother Father	Mother Father
O x O	O x A
A x O	O x B
B x O	A x B
AB x O	B x A
A x A	O x AB
B x B	A x AB
AB x A	B x AB
AB x B	
AB x AB	

TABLE 2. SUMMARY OF OUR MATERIALS COMPARED WITH THE EXPECTED VALUES

a) O x A matings

Mother x Father	Number of Families	Number of Children			
		O		A	
		Observed	Expected	Observed	Expected
A x O	301	282	284.5	430	427.5
O x A	313	320	275.3	369	413.7

$\chi^2 = 6.679$ (calculated by use of the 2 x 2 table).
1 degree of freedom, Probability < 0.01.

b) O x B matings

Mother x Father	Number of Families	Number of Children			
		O		B	
		Observed	Expected	Observed	Expected
B x O	158	142	154.2	214	201.8
O x B	165	190	170.6	204	223.4

$\chi^2 = 5.267$ (calculated by use of the 2 x 2 table).
1 degree of freedom, Probability < 0.05.

of children on the supposition that there were no selection by the ABO incompatibility. As it is apparent from the Table, the values of Chi-square calculated by use of the 2 x 2 table are significantly large both in the O x A and O x B matings. Furthermore, in contrast with the good agreement of observed and expected frequencies of each group of children born from the mating mother A or B x father O, the discrepancies are exceedingly remarkable in the reversed types of mating, indicating that there actually exists a considerably strong selection by the ABO incompatibility. It is calculated that the observed deficiency of A or B children from the incompatible mating is highly significant. It amounts to about 14 per cent of all children (mother O x father A), and about 10 per cent (mother O x father B), and represents a shortage rate of about 23 per cent of A children, or 18 per cent of B children in the mating mother O x father A or B.

NATURAL ABORTIONS AS INDICATION OF INTRA-UTERINE SELECTION BY THE ABO INCOMPATIBILITY

In the above studies it was revealed that there is a shortage of children of certain groups from the incompatible matings. If the elimination of the incompatible children were caused by maternal foetal isoimmunization and occurred at a sufficiently late period of pregnancy for the miscarriages to be recognizable, then certain types of matings should produce more miscarriages than the other. The author and his co-worker (1953) have examined spontaneous miscarriages from the view point of the ABO incompatibility.

The materials were taken from clinic patients who have recently visited the obstetrical department of our University Hospital for the purpose of delivery. If the patient had been pregnant at least more than once in her history, she was counted (at random) into our samples. With each couple we tested their blood groups and the number of times of pregnancy and miscarriages they had had. All miscarriages in question were before the seventh month of pregnancy, and the greater part of them were before the fourth month.

Out of 2,000 couples (approximately) that were tested 425 were of O x A mating and 233 were of O x B mating. The results obtained are summarized in Table 3. It is apparent that the frequency of miscarriages is much higher in the mating mother O x father A than in the mating mother A x father O, and the value of Chi-square calculated by use of the 2 x 2 table is significantly large, so that it can be said in the O x A mating that the compatible couples have less chances of miscarriages than the incompatible. Furthermore, with the O x B mating a similar relation as above can be seen; the mating mother B x father O has less chances of miscarriages than the reversed type of mating.

As miscarriages occur frequently also in the compatible mating of mother A or B x

TABLE 3. INCOMPATIBILITY AND FREQUENCY OF MISCARRIAGES

a) O x A mating

Mating		Number of Times of Miscarriages	Number of Times of Normal Delivery	Total	Mean Number of Pregnancies
Mother Father	Number				
A x O	231	90 (11.79 ± 0.78%)	673	763	3.30
O x A	194	97 (17.07 ± 1.06%)	471	568	2.93

$\chi^2 = 7.522$ (calculated by use of the 2 x 2 table).
1 degree of freedom, Probability < 0.01

b) O x B mating

Mating		Number of Times of Miscarriages	Number of Times of Normal Delivery	Total	Mean Number of Pregnancies
Mother Father	Number				
B x O	137	43 (9.95 ± 0.97%)	389	432	3.15
O x B	96	48 (18.82 ± 1.65%)	207	255	2.66

$\chi^2 = 10.977$ (calculated by use of the 2 x 2 table).
1 degree of freedom, Probability < 0.01.

father O, there are undoubtedly various factors responsible for foetal death aside from incompatibility. However, from above results it can be recognized that the ABO incompatibility in parents is one of the most important factors which might cause miscarriages. Considering the fact that the children of incompatible groups are eliminated through the selection, as above-mentioned, it is probable that the higher frequency of miscarriages in the incompatible matings are due to the including of excess miscarriages of the foetus of incompatible groups. Of course such miscarriages are not thought to be caused by incompatibility alone, but also by some other unknown factors, because there are still many normal children born from the incompatible matings.

It is also of some interest to compare the mean number of pregnancies in the compatible matings with the mean number of pregnancies in the incompatible matings. As it is shown in the Table, the mean number of pregnancies in the former is calculated to be larger than that in the latter with both O x A and O x B matings. The difference, though not yet at a significant level, suggests that selection could occur at the earliest period of pregnancy under conditions unknown to the mother. In addition to this difference, the remarkable discrepancy in the frequency of miscarriage indicates that there should be differential reproductive rates between compatible and incompatible matings in regard to ABO blood groups.

THE ACTION OF SELECTION ON THE ABO ALLELES

It has been found that there actually exists a considerably strong selection by the ABO incompatibility. This fact, from the view point of population genetics, has a very important meaning. Since the genotypes of the eliminated children are always AO or BO, the action of selection against these heterozygotes, because of the simultaneous elimination of an A and an O gene or of an B and an O gene, must work to depress the gene frequencies of the alleles which are less common in the population, as described by Wiener (1942) and Haldane (1942) with the case of Rh alleles. Assuming that, therefore, there did not occur any compensatory factors of another kind for these losses in each generation, the gene frequencies of ABO blood groups in certain races might be expected to change with the passage of time owing to the intra-uterine selection by the incompatibility, even though not subject to race crossing.

In this connection, the data compiled from the results of the above thirteen family

TABLE 4. DISTRIBUTION OF THE ABO BLOOD GROUPS IN JAPANESE OF DIFFERENT GENERATION

Blood Groups	Population of the			
	Parents		Children	
	Number	Per cent	Number	Per cent
O	1,567	30.51 ± 0.43	1,912	31.87 ± 0.41
A	1,948	37.93 ± 0.46	2,254	37.57 ± 0.42
B	1,171	22.80 ± 0.39	1,357	22.61 ± 0.36
AB	450	8.76 ± 0.27	477	7.95 ± 0.24
Total.....	5,136	100%	6,000	100%

investigations are summarized in Table 4, showing the comparison of the distribution of the four blood groups of the parents and of the children. Of course only a slight tendency suggesting the changes of the distribution of the groups could be seen from the Table, but in the course of long period of time, if there were not any compensatory factors, it could be as a result that the gene frequency of O would increase evidently and that of A or B would decrease. However, in order to answer these questions further investigations are necessary.

SUMMARY

In view of the recent recognition of the dangers of maternal foetal isoimmunization, the selective effect caused by the ABO incompatibility of mother and foetus upon the population was examined with Japanese materials.

From the literatures the results of thirteen family investigations were collected. The data covered a period between 1924 until 1952 on 2,709 families with 6,360 children, and attention was focused on the O x A and O x B matings. The results obtained were that, in contrast with the good agreement of observed and expected frequencies of each group of children born from the mating mother A or B x father O, a remarkable elimination of A or B children from the reversed types of mating was revealed, indicating that there exists in fact a considerably strong selection by the ABO incompatibility. It is calculated that the deficiency of A children amounts to about 14 per cent of all children from the mating mother O x father A, and the deficiency of B children amounts to about 10 per cent of all children from the mating mother O x father B.

In order to determine whether this selection could occur as spontaneous miscarriages or not, nearly 2,000 couples who had been pregnant at least more than once were examined from the files of the obstetrical department of the Sapporo University of Medicine. It was found that the frequency of miscarriages is as follows: in the mating mother A x father O; 11.79 $\pm$ 0.78%, mother O x father A; 17.07 $\pm$ 1.06 %, (difference significant at 1 per cent level), mother B x father O; 9.95 $\pm$ 0.97 %, mother O x father B; 18.82 $\pm$ 1.65 % (difference significant at 1 per cent level). This higher frequency of miscarriages in the incompatible matings is considered probably due to the including of excess miscarriages of the foetus of incompatible groups as a indication of intra-uterine selection caused by maternal foetal isoimmunization.

Furthermore, the mean number of pregnancies in the compatible mating was calculated to be larger than the mean number of pregnancies in the incompatible mating with both O x A and O x B matings. The difference did not reach a significant level, but it suggests that selection could occur at the earliest period of pregnancy under conditions unknown to the mother. In addition to this difference, the remarkable discrepancy in frequency of miscarriage indicates that there should be differential reproductive rates between compatible and incompatible mating in regard to ABO blood groups.

The action of selection upon the ABO alleles was discussed from the view point of population genetics, and the data showing the comparison of the distribution of the four blood groups in Japanese of different generation were tabulated. Although only a slight tendency of the changes of the ABO frequencies could be seen within a few

generations, it was suggested that with the passage of time, if there were not any compensatory factors, the gene frequencies of ABO alleles in certain races might be expected to change owing to the intra-uterine selection by the ABO incompatibility.

REFERENCES

HALDANE, J. B. S. Selection against heterozygosis in man. *Ann. Eugen.*, 11: 333–340 (1942).

HIRSZFELD, L. AND ZBOROWSKI, H. Ueber die Grundlagen des serologischen Zusammenlebens zwischen Mutter und Frucht. *Klin. Wschr.*, 5(17): 741–744 (1926).

KOBAYASHI, T. Statistische Beobachtung der Bluttypenverteilung im ABO System bei Japanern. 11 Mitt. *Hanzaigaku-Zasshi*, 14(5): 727–735 (1940) (in Jap.).

LEVINE, P. Serological factors as possible cause in spontaneous abortions. *J. Hered.*, 34: 71–80 (1943).

MATSUNAGA, E. Intra-uterine selection by the ABO incompatibility of mother and foetus. *Proc. Japan Acad.*, 29: 399–403 (1953).

MATSUNAGA, E. AND ITOH, S. Intra-uterine selection by the ABO incompatibility of mother and foetus. 2nd Report. *Proc. Japan Acad.*, 29: 529–531 (1953).

WATERHOUSE, J. A. H. AND HOGBEN, L. Incompatibility of mother and foetus with respect to the iso-agglutinogen A and its antibody. *Brit. J. Social Med.*, 1: 1–17 (1947). Cited from RACE, R. R. AND SANGER, R.: Blood Groups in Man (1950).

WIENER, A. S. Rh factor and racial origins. *Science*, 96: 407–408 (1942).

Data on Linkage of Ovalocytosis and Blood Groups[1]

T. FUJII, W. C. MOLONEY[2] AND N. E. MORTON[3]

Atomic Bomb Casualty Commission, Hiroshima, Japan

LINKAGE of the gene for ovalocytosis (oval red cell anomaly) and the Rh blood group system has been reported by Goodall et al. (1953, 1954), Lawler and Sandler (1954), and Marshall et al. (1954). During the course of an investigation of late radiation effects of the atomic bomb in Hiroshima, ovalocytosis was encountered in five Japanese families (Fujii and Tsuchitori, 1953). A study of possible linkage of the oval red cell anomaly with several test traits was undertaken.

RESULTS

In one of the families only one individual could be examined. Pedigrees of the other four families are given in Figure 1. Blood was typed for ABO, MN, Rh and Kell. Taste sensitivity was determined by the use of phenylthiocarbamide test papers. The blood groups, taste sensitivity, presence or absence of ovalocytosis, and other details are shown in the appendix.

The red cells in all the cases reacted to anti-D and did not react to anti-Kell. No parent was known to be both heterozygous for taste sensitivity and affected with ovalocytosis. Therefore, of the linkage testers used, only the ABO blood group, the *C*, *c*, and *E* reactions of the Rh system, and the MN group are informative in these pedigrees. Calculations of linkage scores are shown in Table 1, using the u statistics of Fisher (1935) as modified by Finney (1940).

Two of the linkage scores require comment. Family O. M. II. 1,2 is A D x ?, with all O progeny, so that as in double backcrosses, there is a one-to-one correspondence between progeny phenotype and genotype. The mating is either a double backcross or a single backcross, with probabilities p_1 and $1 - p_1$, respectively. Since $a + c = 0$, the score and information (Finney, 1941, equations 4.1 and 4.11) are

$$\lambda = [(b - d)^2 - (b + d)]/2 = u_{11}/2$$

$$\kappa = (b + d)(b + d - 1)/2 = \omega_1$$

As expected, the scoring is the same as if the mating had been known to be of the double backcross type. In family M. K. II. 7,8, neither parent was tested and the progeny are R_1R_2 and R_1R_1. The possibilities to be considered are that the parents

Received August 26, 1954.

[1] This work was sponsored by the Atomic Bomb Casualty Commission, Field Agency of the National Academy of Sciences-National Research Council, with funds supplied by the United States Atomic Energy Commission.

[2] Present address: Boston City Hospital, Boston, Massachusetts.

[3] Present address: Department of Genetics, University of Wisconsin, Madison, Wisconsin.

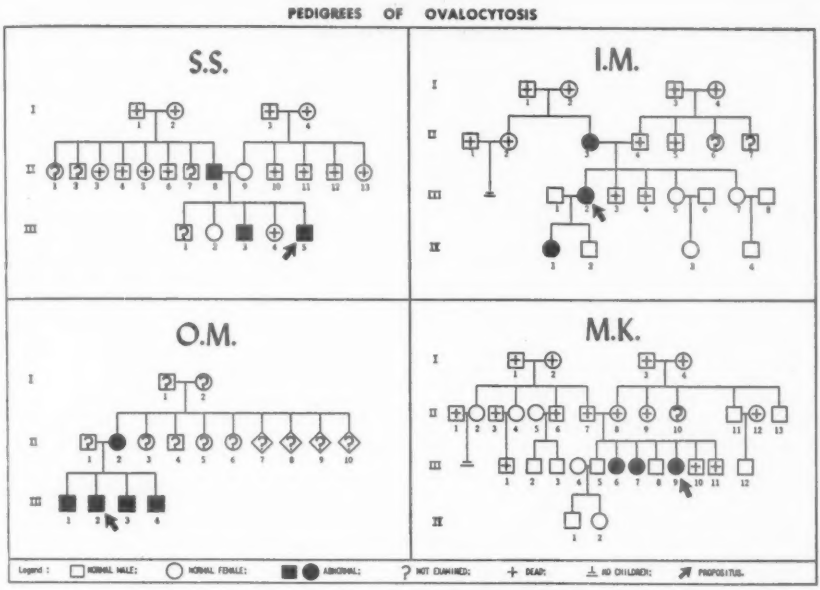


FIG. 1

TABLE 1. LINKAGE SCORES

Tester	Parents	Finney Type	a	b	c	d	s	λ	k
MN	M. K. II. 7, 8	4	1	1	—	2	4	0	6
ABO	O. M. II. 1, 2	1a	—	4	—	—	4	6	6
	I. M. III. 1, 2	3	—	1	1	—	2	1	1
	S. S. II. 8, 9	3	2	—	—	1	3	3	3
Rh	M. K. II. 7, 8	3a	3	—	1	1	5	.9	2.6
	S. S. II. 8, 9	1	1	1	1	—	3	−1	3

Symbols refer to Finney (1940).

were R_1R_1 x R_1R_2, R_1R_2 x R_1R_2, and R_1 "R" x R_1R_2, where "R" is any non-R_1, non-R_2 chromosome. According to Chown et al. (1946), the frequencies of the R_1, R_2, and "R" chromosomes in Japanese are about .6, .3, and .1, respectively, so that the posterior probabilities of the three matings are 96/103, 6/103, and 1/103. This mating type is more complex than any considered by Finney (1941), but may be handled by neglecting the last possibility. Then $p_1 = 8/17$, $p_2 = 1/17$, $\lambda = .9$, $v_1(x, y) = 20$, $v_1(x, z) = v_1(x, 0) = 12$, and $\kappa = 2.6$.

CONCLUSIONS

These families reveal no significant linkage of the gene for ovalocytosis to the genes for the ABO, Rh, or MN blood groups. In family S. S. II. 8,9, where the male

APPENDIX

KEY TO RH REACTIONS

CDe = C + c − D + E −	CcDE = C + c + D + E +
CDE = C + c − D + E +	cDe = C − c + D + E −
CcDe = C + c + D + E −	cDE = C − c + D + E +

No.	Sex	Year of birth	Ovalocytosis	ABO	MN	Rh	PTC
S. S. II. 8	M	1898	+	AB	N	cDE	+
S. S. II. 9	F	1907	−	A	N	CDe	+
S. S. III. 2	F	1927	−	AB	N	CcDE	+
S. S. III. 3	M	1930	+	A	N	CcDe	+
S. S. III. 5	M	1937	+	A	N	CcDE	+
I. M. II. 3	F	1895	+	A	M	CDe	−
I. M. III. 1	M	1915	−	B	M	CcDE	−
I. M. III. 2	F	1921	+	AB	M	CDe	−
I. M. III. 5	F	1929	−	AB	M	CDe	+
I. M. III. 7	F	1932	−	A	M	CDe	−
I. M. IV. 1	F	1944	+	AB	M	CDe	−
I. M. IV. 2	M	1947	−	B	M	CDe	−
O. M. II. 2	F	1917	+	A	N	CDe	+
O. M. III. 1	M	1941	+	O	N	CDe	+
O. M. III. 2	M	1943	+	O	N	CDe	+
O. M. III. 3	M	1945	+	O	N	CDe	+
O. M. III. 4	M	1949	+	O	N	CDe	+
M. K. III. 5	M	1926	−	A	N	CcDE	−
M. K. III. 6	F	1929	+	A	N	CDe	−
M. K. III. 7	F	1932	+	A	MN	CDe	−
M. K. III. 8	M	1934	−	A	N	CDe	−
M. K. III. 9	F	1936	+	A	M	CDe	−

parent is affected, there is at least one recombinant between the genes for ovalocytosis and the Rh complex. For a valid analysis of linkage, it is essential that data be reported without regard for whether they suggest linkage or not. The amount of information in these data is small, and should be evaluated in connection with other linkage studies on ovalocytosis.

The sera used in this investigation were kindly provided by Dr. John Elliot of the Blood Bank of Dade County, Miami, Florida, and the PTC test paper by Dr. Chozo Oshima of Osaka University.

REFERENCES

CHOWN, B., Y. OKAMURA, AND R. F. PETERSON. 1946. The Rh types in Canadians of Japanese race. *Can. J. Res.* 24: 135–143.

FINNEY, D. J. 1940. The detection of linkage. *Ann. Eugen.* 10: 171–214.

FINNEY, D. J. 1941. The detection of linkage. III. Incomplete parental testing. *Ann. Eugen.* 11: 115–135.

FISHER, R. A. 1935. The detection of linkage with "dominant" abnormalities. *Ann. Eugen.* 6: 187–201.

FUJII, T. AND K. TSUCHITORI. 1953. Hematological, statistical, and genetic study of ovalocytosis. *Acta Haematologica Japonica* (in the press).

GOODALL, H. B., D. W. W. HENDRY, S. D. LAWLER, AND S. A. STEPHEN. 1953. Data on linkage in man: elliptocytosis and blood groups. II. Family 3. *Ann. Eugen.* 17: 272–278.

GOODALL, H. B., D. W. W. HENDRY, S. D. LAWLER, AND S. A. STEPHEN. 1954. Data on linkage in man: elliptocytosis and blood groups. III. Family 4. *Ann. Eugen.* 18: 325–327.

LAWLER, S. D., AND M. SANDLER. 1954. Data on linkage in man: elliptocytosis and blood groups. IV. Families 5, 6 and 7. *Ann. Eugen.* 18: 328–334.

MARSHALL, R. A., R. M. BIRD, H. K. BAILEY, AND E. BECKNER. 1954. Genetic linkage between ovalocytosis and the Rh blood type. *J. Clin. Invest.* 33: 790–793.

Comments on the Rate of Mutation to Chondrodystrophy in Man

HERMAN M. SLATIS

Department of Genetics, McGill University, Montreal, Quebec

RECENT studies of the rate of mutation at various loci in man, a summary of which may be found in the paper by Neel and Falls (1951), have greatly increased our knowledge of the genetics of our own species. However, some of these estimations of the mutation rate may be in error in important ways. Of late, the data of Mørch (1941) on chondrodystrophy have been the subject of comments by Popham (1953) and Krooth (1953). Krooth points out that relative to a condition such as chondrodystrophy, in which most of the affected individuals are sporadic cases in otherwise normal families, there is a strong bias in the calculation of the fertility of affected individuals compared with the fertility of normal sibs. This bias is due to the fact that there is a positive correlation between the family size into which an individual is born and the family which he will raise. Although the average mutant individual who occurs in a large family may have many children when compared with the average mutant who occurs in a small family, the average number of children of all mutants will be intermediate in size. However, the mutant from a large family will have many sibs, with a high average number of children per sib, and the few sibs of the mutant in a small family will do little to lower the high average of the family size among sibs of mutants. For this reason a comparison of the average number of children of affected individuals and their sibs will make the affected individuals seem to have smaller families even if they do not. Krooth has noted that one can compare the average number of children of affected persons and their normal sibs by grouping all individuals according to the family size into which they were born. An objection to this practice would be the lack of normal sibs in one child families.

One may add to Krooth's observations that the bias in calculating comparative fertility will occur for any trait, since the proportion of normal sibs of affected individuals will increase as family size increases and the normal sibs are, therefore, drawn from larger families than the affected individuals. For example, with complete ascertainment of a sex-linked recessive such as hemophilia, in which comparative fertility has been measured by Andreassen (1943), there would be zero normal male sibs in one male child families, 0.5 as many normal male sibs as affected individuals in two male child families, and this proportion would approach an asymptote of one male sib per affected individual as family size increases. If all sibs of hemophiliacs are counted, or if dealing with an autosomal recessive condition, the number of normal sibs per affected individual increases from zero in one child families to 0.75 in two child families and approaches an asymptote of 3.0 as family size increases.

Krooth follows his interesting observations on family size by noting that chondrodystrophics tend to come at the end of their sibships (Mørch's data confirm that this

Received March 5, 1954.

is strikingly so), but then he states that "Hence among contemporary cases the achondroplasics will on the whole be older than their sibs, and therefore parents of larger families than if they and their sibs average about the same age." Of course the word "older" should read "younger", and the chondrodystrophics will have a smaller chance of completing their families than their sibs. Thus, instead of balancing the bias due to comparing the family size of normal sibs with that of the affected individuals, as Krooth suggests, these two biases will reinforce each other and the estimated fertility of chondrodystrophics will be much lower than the true value.

Instead of relative fertility, there is a more reasonable method of estimating the proportion of the chondrodystrophy genes in the population which have come from the preceding generation as opposed to those which are mutants. If we assume that the adverse selection connected with chondrodystrophy is not due to a lower life expectancy, but to a lower fertility, then the proportion of mutant individuals in the population is twice the mutation rate. At the time of Mørch's survey (1941) there were 86 chondrodystrophics living in Denmark. Seven of these had inherited the disease from a parent, leaving 79 persons who may be considered to be primary mutants. With the population of Denmark at approximately 3,800,000, this would mean that mutations had occurred among 79 of the 7,600,000 genes which had been inherited in Denmark, putting the mutation rate at about 1:100,000.

A mutation rate of 1:100,000 is about one-fifth that which has been estimated by Haldane (1949). The difference is due to the fact that Haldane has accepted Mørch's statement that about 80 per cent of all chondrodystrophics die within the first year of life. There is some difficulty in accepting this statement. Mørch's figure of 80 per cent is based on the analysis of only ten cases. Of these ten cases, eight appeared to be primary mutants, and six of these were stillborn or died within the first thirty-eight hours of life. In Mørch's total data, of the fifteen chondrodystrophics who inherited the condition from a parent, none were stillborn or died within this same critical period of life. The unusual distribution of six out of eight mutant individuals dying at or immediately after birth as opposed to none out of fifteen inherited cases dying within the same period would occur by chance only once in 3605 times, according to the "exact method" of Fisher (1950). The objection could be made that my figure has been selected for those cases which have died within the first thirty-eight hours of life. If the first year of life had been chosen, as Mørch has done to calculate the infant mortality of chondrodystrophics, then one more of the spontaneous cases (dead at eleven months) and two of the inherited cases (dead at four and at eight months, respectively, must be listed among the deaths and the probability of so great a deviation from chance or greater (in this direction only) would be only one in 956. An entirely different bias occurs in the inclusion of five cases from a Swedish family of chondrodystrophics, since they were included in Mørch's paper solely because the family shows the condition in three generations. Still another source of error is the selection of inherited cases whose chondrodystrophic parent died before the beginning of this survey. Among the Danish material there are two such cases with one chondrodystrophic child each. Since chondrodystrophic parents of their generation who did not leave long lived chondrodystrophic children have not been included, these cases introduce a bias. These last two biases bring up the frequency of viable inherited

chondrodystrophy. Even if these seven persons are omitted from consideration, which is an overcorrection, there is still only a chance of one in 286 that this distribution is random if death immediately after birth is considered, and a deviation this great or greater would occur only one time in forty-nine if death within the first year of life is considered. A conceivable reason for the apparent difference in viability between sporadic and inherited cases might be that many of the sporadic cases are mutations to a less viable allele at the locus or that the chondrodystrophy allele is normally only slightly viable but other genes may modify it, and since the survival of a mutant is dependant upon his having such genetic modifiers, his children will have a greater than average chance of having such modifiers too.

An entirely different possibility is that the chondrodystrophic children who were stillborn or who died immediately after birth were suffering from some other condition which looks like chondrodystrophy but which is not due to a mutation at this locus. They might be mutants at some other locus, or they might be phenocopies. The possibility of phenocopies, individuals who seem to have the same condition as a known mutant but whose ailment is due to an environmental accident, is very plausible. We must assume that the phenocopy would almost always have other things wrong too and would usually be lethal, while the mutant individual would have the limited disability of shortened extremities. This would explain the fact that chondrodystrophy either causes death at birth or not at all.

It may be noted that Mørch's data show an excess of normal births among the children of chondrodystrophics over the one-half which is expected on the basis of simple genetic theory. Haldane (1949) has selected the Swedish material which emphasises this and has omitted the related material which would operate in the opposite direction, which biases his figure of P at about 0.03. However, the Swedish material should be omitted from all calculations of this nature and so should the two cases among the Danish material in which the parent chondrodystrophic died long before these data were gathered. This leaves 17 normal and 8 chondrodystrophics, which deviate from a 1:1 ratio with a P value of a little more than 0.10. Although this is not significant, it is a deviation in the same direction as would be expected if a few of the chondrodystrophic parents were not mutants but phenocopies. A more extensive collection of data should clarify this point.

Although Mørch has carefully screened from his material a number of conditions which would be mistaken for chondrodystrophy, there is, of course, the possibility that chondrodystrophy is not a single ailment but many. If there were several loci which would produce this sort of phenotype, the mutation rate would be spread over a number of loci and the mutation rate per locus would be less than the rate which has been calculated. Hemophilia, which has long been assumed to be due to mutation at a single locus, has recently been divided into two conditions, true hemophilia and Christmas disease, by Biggs *et al.* (1952). Although the two conditions are similar clinically and genetically, they are so different biochemically that two separate loci are almost certainly involved. Therefore, the mutation rate for hemophilia which has been calculated by Haldane (1949) is somewhat higher than the value at the hemophilia locus because of the inclusion of the mutation rate at the Christmas disease locus.

There is the distinct possibility that chondrodystrophy is not due to a point mutation, but, as Haldane (1949) has suggested to account for the possible failure to segregate properly, it may be due to a chromosomal abnormality. Proper segregation may be occurring in chondrodystrophics, but the striking increase in "mutation" to chondrodystrophy as maternal age increases could be explained as the effect of an increasing failure of chromosomal disjunction with increasing maternal age, rather than as an increase in point mutation with age. It may be noted that these problems lend themselves to solution by a variety of means such as cytological study of chondrodystrophics, the collection of more data on human cases, and the comparison of this condition in humans with similar conditions in other mammals.

SUMMARY

1. The measurement of fertility by a direct comparison of the average number of offspring of affected individuals with the average number of offspring of their sibs will always be biased if the families concerned are chosen because they contain at least one affected child.

2. The measurement of fertility is biased further in the same direction in chondrodystrophy because mutant individuals tend to come late in sibship rank.

3. It is suggested that the mutation rate to chondrodystrophy is about 1:100,000, which is about one-fifth of previous estimates. The previous values are considered to have been in error because they included data on a phenotypically similar condition, possibly a phenocopy, which is usually lethal within a few hours of birth.

4. If chondrodystrophy is due to mutation at more than one locus, which appears to be the case with hemophilia, or if some of the "phenocopies" survive to adult life, the calculated mutation rate will be too high.

5. The maternal age effect of mutation to chondrodystrophy might be due to a failure of chromosomal disjunction, and this ailment might be due to a chromosomal imbalance, rather than point mutation.

REFERENCES

ANDREASSEN, M. 1943. Haemofili i Danmark. *Opera Ex Domo Biol. Hered. Human. Univ. Hafn.* 3: 1–168.

BIGGS, R., DOUGLAS, A. S., MACFARLANE, R. G., DACIE, J. V., PITNEY, W. R., MERSKEY, C. AND O'BRIEN, J. R. 1952. Christmas disease. *Brit. Med. Jour.* 2: 1378–1382.

FISHER, R. A. 1950. *Statistical Methods for Research Workers.* 11th Ed. New York: Hafner.

HALDANE, J. B. S. 1949. The rate of mutation of human genes. Proc. 8th Int. Cong. Genetics (Supplement to Hereditas) pp. 267–273. Lund: Berlingska Boktryckeriet.

KROOTH, R. S. 1953. Comments on the estimation of the mutation rate for achondroplasia. *Am. J. Human Genet.* 5: 373–376.

MØRCH, E. T. 1941. Chondrodystrophic dwarfs in Denmark. *Opera Ex Domo Biol. Hered. Human. Univ. Hafn.* 3: 1–200.

NEEL, J. V. AND FALLS, H. F. 1951. The rate of mutation of the gene responsible for retinoblastoma in man. *Science* 114: 419–422.

POPHAM, R. E. 1953. The calculation of reproductive fitness and the mutation rate of the gene for chondrodystrophy. *Am. J. Human Genet.* 5: 73–75.

Syndactyly of the Ring and Little Finger

OLA JOHNSTON AND VERNON V. KIRBY, JR.

Department of Biology, North Texas State College, Denton, Texas

A PREVIOUS investigation of anomalies of the hands and feet included a section on various types of syndactyly (Johnston and Davis, 1953) but no case of syndactyly of the ring and little fingers was included.

Bell (1931) described syndactyly of the fourth and fifth fingers in each hand with bony fusion in the terminal phalanx only, and with the middle phalanx of the little finger being very short or absent. Complete syndactyly of the ring and little fingers on both hands of a family was reported by Collette (1954). The condition arose as a mutation in the propositus, and its inheritance is probably due to a dominant gene.

The propositus of the family reported here lives in a near-by town. An interview with the man revealing syndactyly of the ring and little fingers produced the pedigree. In the pedigree (figure 1) the grandfather I-1 of the propositus, III-19, was the first known individual to show syndactyly, but the manner of expression is not known.

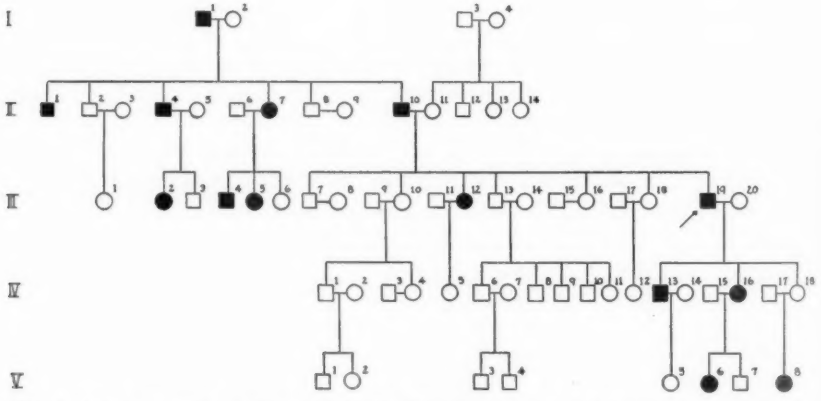


FIG. 1. A five generation pedigree of a family showing syndactyly of the ring and little fingers.

The propositus shows complete syndactyly of fingers four and five (plates 1 and 2). Finger four of each hand is flexed dorsally and abducted toward finger five. The nails of the syndactylous fingers on both hands are fused medially except near the beds, indicating that they were of separate origin. The x-ray photographs, plates 3 and 4, show the absence of phalanx two in both the right and left fifth fingers, and fingers four and five of each hand show only fleshy fusion.

Of the remaining descendants of I-1 who show syndactyly, there are four varia-

Received October 1, 1954.

PLATE 1

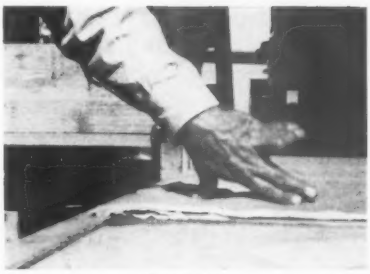


PLATE 2

PLATE 1. Dorsal view of the hands of the propositus, III-19, showing complete syndactyly of the ring and little fingers.

PLATE 2. View of left hand of propositus showing flexion and abduction of the ring finger.

PLATE 3

PLATE 4

PLATE 3. X-ray photograph of right hand of propositus, III-19; dorsal view.

PLATE 4. X-ray of left hand of propositus, III-19; dorsal view.

tions. The partial fusion of the proximal half of the fourth and fifth fingers of the left hand only occurs more often in females than in males. Three males, II-1, II-4, and II-10, expressed the anomaly by partial syndactyly of the fourth and fifth fingers of both hands, with the distal ends of the fingers separated. One male, III-4, and two females, II-7 and III-12, demonstrated syndactyly of the fourth and fifth fingers of both hands with the fourth finger flexed dorsally and towards the fifth finger. The extreme variation was represented in a female, V-6, by complete syndactyly of the third, fourth, and fifth fingers of the right hand, and complete syndactyly of the

fourth and fifth fingers and partial syndactyly of the proximal half of the third and fourth fingers of the left hand.

A son, IV-13, of the propositus had syndactyly accompanied by a rudimentary middle phalanx of the fifth finger of each hand. It appears that shortened or missing phalanges are associated with the anomaly. These findings are in agreement with those of Bell: that rudimentary phalanges may accompany and complicate syndactyly.

A female, V-8, showed the anomaly when neither parent showed it, but the maternal grandfather, III-19, had syndactyly of the fourth and fifth fingers.

The syndactylous condition of the fingers did not interfere with the use of the hands. Fingers of II-4 were separated surgically, but became useless after separation, and the man later had the separated fingers amputated for they interfered with the use of his hands. The result of the surgery seems to indicate that while the bones of the syndactylous fingers were separate they were controlled by the same group of muscles.

The pedigree of the family presented suggests that syndactyly of the fourth and fifth fingers is transmitted as an autosomal dominant gene with incomplete penetrance and varying expressivity.

The inheritance of syndactyly reported by Collette showed complete fusion between the ring and little finger of each hand, with no variation. The conclusion reached was that the anomaly is probably due to an autosomal dominant gene.

SUMMARY

In the five-generation pedigree syndactyly appears to be inherited as a simple dominant autosomal gene with incomplete penetrance and variation in expression. The pedigree of the family studied adds additional evidence of the inheritance of syndactyly of the ring and little fingers. Missing or rudimentary middle phalanges of the fifth finger appear to be associated with the anomaly.

REFERENCES

Bell, Julia. 1931. Three further cases of hereditary digital anomaly. *Ann. Eugen.* 4: 233–237.

Collette, A. T. 1954. A case of syndactylism of the ring and little fingers. *Am. J. Hum. Gen.* 6: 241–243.

Johnston, Ola and Davis, R. W. 1953. On the inheritance of hand and foot anomalies in six families. *Am. J. Hum. Gen.* 5: 256–372.

BOOK REVIEWS

Wirksame Faktoren im Leben des Menchen Beobachtungen an ein-und zweiigen Zwillingen durch 25 Jahre

By O. F. v. Verschuer, Wiesbaden, Franz Steiner Verlag G M B H, 1954, Pp. 288 + 105.

THIS paper backed book records the author's unique and interesting investigations of 150 like-sexed twins in southwestern Germany, covering a period of 25 years. Dr. v. Verschuer has a long and distinguished record in twin research, and is especially well known for his earlier pioneer studies (in collaboration with Diehl) on tuberculosis in twins.

Of the 150 pairs of twins investigated, 100 pairs were monozygotic and 50 pairs were dizygotic. The twins were studied four times, first in 1924–25, again in 1926–27, still again in 1936, and finally in 1949–50. When the last investigation was made, only one member of each of 34 pairs still survived, and both members of 18 pairs were dead. Among the male twins 29 (22%) were killed during World War II. The average age of the twins was 16 years when the first investigation was made.

Following a brief introductory chapter, 96 pages are devoted to the biographies of each pair. Separate chapters take up each of the following topics: longevity and causes of death, diseases, marriage and offspring, physical development, mental and personality development, discussion of the findings, and summary. Photographs of the twins, taken at different age levels during the investigations, require 70 pages of the book. The anthropometric data are recorded in detail and comparisons of the various types of data are graphically illustrated by several figures.

The monozygotic and dizygotic twins showed no significant intra-pair differences with respect to life span either in pairs where both had died or in those pairs where one member still survived. Furthermore, no significant differences were observed between the two types of twins with respect to comparative degrees of concordance and discordance in the pooled incidence of all types of diseases, discordance greatly outweighing concordance.

Intrapair differences in physical measurements at the first and last investigations were compared, greater differences at the last investigations being interpreted as an indication of the effectiveness of environment. Verschuer classified the monozygotic twins into two categories as follows: (1) those pairs both of whose members lived similar lives and (2) those pairs whose members were exposed to somewhat different conditions, such as markedly different socio-economic or professional status, severe illness in only one member of the pair, or number of children. He coined the term *peristatischen Faktoren* to describe greater intrapair environmental differences of twins in category 2. Marked increases in intrapair differences of twins in this category, as compared with relative stability among twins in category 1, were attributed to "peristatic" factors. Body weight was greatly affected, whereas the skeletal and muscular systems were relatively uninfluenced by them.

The author believes that slight intrapair differences brought about during the embryological development of monozygotic twins may leave their imprints throughout their entire lives, to such an extent as to account for those pairs whose members may take up different occupations, or attain quite different degrees of social and economic success. He states that while many important differences in human beings, with respect to disease, life span, physical and mental variations, may definitely be attributed to heredity in some instances, and to environment in others; some of them do not clearly appear to be due to either heredity or environment.

It occurs to this reviewer that many of the unexplained differences may be attributed to interactions of heredity and environment. Plasticity of response to environment is in part genetically determined, and there may be situations where the phenotype of the heterozygote depends upon the environment, whereas the phenotype of the homozygote is dependent upon the genotype. Under such circumstances monozygotic and dizygotic twins may exhibit similar degrees of concordance and discordance. This could be one reason why in Verschuer's investigation the two types of twins manifested such similar degrees of concordance-discordance ratios with respect to disease and life span.

This book is essentially a descriptive account, rather than a technical analysis of the investigation. No objective psychological tests were employed, and only the simplest kinds of statistics were used for interpreting the data. But the account is of unusual importance, because relatively few longitudinal or life-long studies of twins have been made. More longitudinal studies are needed, and a report of this sort may attract more wide spread interest than a formidable statistical analysis. The photographs of the twins taken at different age levels tell fascinating stories which can be read by all. The raw data are given, and are thus made available to those who may care to give them further treatment. This fascinating volume should be called to the attention of all students of human genetics.

DAVID C. RIFE
Ohio State Univesrity

Le Sang Des Peuples

By N. Lahovary. Pacomhy, Ed., Paris, 1954. 286 pp.

BLOOD grouping has become an important fundamental technique with which physical anthropologists and geneticists must be familiar. Studies on the distribution of the blood types, especially since the discovery of the Rh-Hr types, have thrown considerable light on the interrelationship among different human populations. Unfortunately, in this field, just as in other fields, a good deal of misinformation is being published all the time, and the average physical anthropologist is probably not qualified to recognize which articles or books are reliable in a subject so foreign to his daily work. The book by Lahovary, for example, provides an outstanding demonstration of how little information and how much misinformation can be crowded into a 286 page monograph.

Lahovary's monograph is devoted to the use of his so-called "Index of Difference," in an attempt to show relationships among populations. The example he cites in his book will serve to demonstrate how his index is calculated. Let us consider two populations, one with the blood group distribution O 27, A 53, B 13, AB 7, and the other with the distribution O 45, A 40, B 10, and AB 5. The author takes the absolute values of the differences between the corresponding frequencies and sums them, thus: 18 + 13 + 3 + 2, to obtain 36 as the Index of Difference between these two populations. He recommends the use of similar indices for the M.N types, Rh-Hr types, and for other blood types and states that by summing the indices one can then obtain a single value which takes all the systems into account. There is no doubt that Lahovary's index is simple, but this appears to be its only virtue, namely, that it requires no knowledge of blood grouping, genetics, anthropology, or biometrics, because its calculation entails only elementary arithmetic. To those who understand the rudiments of blood grouping, it soon becomes clear that Lahovary himself has little or no understanding of the subject, since, for example, on page 23 he states, "Aux trois phénotypes M, N, MN, correspondrent par consequent seulement deux genotypes: MM, NN."

The fallacy of the Index of Difference will be obvious to anyone having even an elementary understanding of blood grouping, genetics and biometrics. In the case of the three M-N types, the single value for the frequency of gene *M*, for example, has been used in the past to show very simply relationships among populations having different distributions of the three M-N types. Moreover, from the frequency of gene *M* (or *N*) the distribution of the three types in the populations is readily recalculated. Lahovary's Index of Difference, on the other hand, gives no insight into the blood type distribution of a population, but merely in a rough way indicates the degree of difference between two populations. Moreover, two populations with quite different distributions of the M-N types may have the same Index of Difference with respect to a third population taken as a point of reference. This has led Lahovary to construct elaborate but meaningless diagrams, such as those on pages 206 and 211, which serve to confuse one further rather than to clarify. Moreover, the number of Indices of Difference increases rapidly with the number of populations being compared, so that, for example, if 100 different populations are compared, one would have to calculate and manipulate 4950 indices, none of which gives any insight into the actual distribution of the types. On the other hand, the 100 simple values for the frequencies of gene *M* would give complete information regarding the M-N type distribution, and at the same time show clearly and simply the relationships among the populations. Instead of making 4950 two-by-two comparisons, all that is necessary is to arrange the populations according to the magnitude of the frequency of gene *M* to see at a glance the relationship among them.

When it comes to the more complex A-B-O groups, Lahovary's difficulties with his index are multiplied, and his diagrams become more complex and confused. He objects to the use of gene frequency analysis, evidently because this is too esoteric, and argues that his index calculated from phenotype frequencies is simpler. But for some obscure reason, he presents tables showing A-B-O gene frequencies on pages 175 to 179. Moreover, in a footnote to page 35, he derives novel but incorrect formulae for calculating the A-B-O gene frequencies. The subgroups of A are mentioned merely in passing, which is fortunate, because any attempt to include them when calculating the index would only befuddle the picture further. As to be expected, the treatment of the more complex Rh-Hr types is totally jumbled, and in the tables on pages 226 to 230, genes, genotypes and phenotypes are confused beyond repair. Nowhere in the monograph does Lahovary make any attempt to apply statistical analysis to determine the significance of the differences among the indices calculated by his method.

In view of the considerations which have been presented, Lahovary's book cannot be recommended.

A. S. WIENER
Brooklyn, N. Y.

Adaptation in Micro-organisms

Third Symposium of The Society for General Microbiology, London, 1953. Edited by R. Davies and E. F. Gale. New York: Cambridge University Press, 1953, pp. 339, illus. and plates, $6.

THIS volume contains the papers and discussions of the third symposium of The Society for General Microbiology, held at the Royal Institution, London, in April 1953. An interesting feature of the conference was that the papers of the fifteen invited participants were printed and circulated in gally proof to all members of the Society some two weeks before the conference; at the meeting the papers were taken as read, and the time was devoted to discussion, questions, and argument. Consequently, many of the printed discussions contain well considered material and make significant contributions to the problems in question.

In an introductory paper Stanier gives a concise outline of key points connected with the adaptation of microorganisms. In the next paper, consisting of observations on bacterial adaptation by Dean and Hinshelwood, some concession is made to the view that genetic mutations may be responsible for adaptation in microorganisms, but the main emphasis is placed on adaptation through some ill defined process of "training." A paper discussing drug resistance, given at a later session by Abraham, is strongly biased toward Hinshelwood's view; and two other papers on the same topic by Barber and by Mitchison avoid controversial issues. Pontecorvo, who did not present a formal paper, represents the geneticist's point of view strongly in the discussions. In particular, he stresses the importance of heterokaryosis and of mitotic recombination as possible mechanisms of adaptation in fungi.

Evidence that both genic and cytoplasmic components of a cell are involved in certain adaptations is presented by Slonimskik who describes work on the action of acridines in enzymic adaptation in yeasts, and by Beale, who discusses four kinds of adaptive change in *Paramecium* that can occur as a consequence of cytoplasmic reorganization—without gene mutation, but in which, nevertheless, genes play an important part. Pollock, in discussing a cyclic system of adaptive enzyme formation to explain the kinetics of penicillinase synthesis, also presents his speculative hypothesis on the role of enzyme adaptation in genetics. Other papers relating to enzymic adaptation deal with: the effect of various substrates on adaptation in the citric acid cycle in *Aerobacter aerogenes* (Ravin); the nature of the precursor in the induced synthesis of enzymes (Spiegelman and Halvorson); specific control of the synthesis of adaptive and constitutive enzymes (Cohn and Monod); and the effect of temperature on enzymic adaptation, growth, and drug resistance (Knox).

The remaining three papers discuss the influence of bacteriophage on bacterial variation and evolution (Hewitt), adaptation in thermophiles (Clegg and Jacobs), and ecological adaptations in fungi (Brown and Wood). This volume contains many good ideas, and makes very interesting reading.

M. DEMEREC
Carnegie Institution of Washington

Errata

THE following corrections should be made in the paper by William C. Boyd, entitled "Shortened Maximum Liklihood Estimation of Rh Gene Frequencies" which appeared in volume 6, number 3 (September 1954 issue) of this Journal.

Page 304, unnumbered table, R_2 = Cde should read R_2 = cDE; R′ = CDe should read R′ = Cde. Page 305, eighteenth line under table 1, "put" should read "out". Page 318, reference 11, "Methematical" should read "Mathematical".

BIBLIOGRAPHY OF HUMAN GENETICS

Prepared by

DR. V. RAE PHELPS

P. O. Box 522, East Lansing, Michigan

THIS SECTION is a continued list of references to recent and current articles and books which may be of interest to students of Human Genetics. An attempt has been made and is being made to make the list both up to date and complete, but to do so is a difficult task. Everyone who finds the list useful and considers a complete one desirable, can be of help by sending to the bibliographic editor, at the address given above, any recent reference which has been missed or references to papers in press. The bibliographic editor wishes to take this opportunity to thank the many people who have been and it is hoped, will continue to be of help in this way.

AGGELER, P. M., WHITE, S. G., & SPAET, T. H. 1954. Deuterohemophilia: plasma thromboplastin factor B deficiency: plasma thromboplastin component (PTC) deficiency, Christmas disease, hemophilia B. *Blood*, Balt. 9(3): 246–253.

ALLISON, A. C. 1954. Protection afforded by sickle-cell trait against subtertian malarial infection. *Brit. M. J.* No. 4857: 290–294.

ANASTASI, A. 1953. Individual differences. *Annual Rev. Psychol.* 4: 137–156.

ANONYMOUS. 1953. Discussão de casos clínicos: caso No. 17: eritrofalcemia em branca. [Discussion of clinical cases: No. 17: sickle cell anemia in a white woman.] *Arq. brasil. med.* 43(7–8): 307–309.

ARRIGONI, G., & LOVATI, G. 1953. Studio genetico del rene polocistico; nota preventiva. [Genetic studies on the polycystic kidney; preliminary note.] *Arch. ital. urol.* 26(3): 179–183.

ASDELL, S. A. 1953. The relationship of fertility to intelligence. *Ann. ostet. gin.* 75(6): 885–890.

AUERBACH, C. 1954. After-effects of radiation and chemicals on chromosomes and genes. *Brit. J. Radiol.* 27(314): 122–124.

AUVERT, B. 1953. Un cas curieux de malformation pupillaire héréditaire. [A rare case of hereditary malformation of the pupil.] *Bull. soc. opht. France* No. 6: 586–592.

BELTRÁN, J. C. 1943. Hemofilia. *Arch. pediat. Uruguay* 24(11): 731–748.

BÉRARD, P. V. 1953. Dégénérescence familiale de la macula, a propos de trois cas. [Familial degeneration of the macula, with three cases.] *Bull. soc. opht. France* No. 5: 499–504.

BERRY, H. K. 1953. Variations in urinary excretion patterns in a Texas population. *Am. J. Phys. Anthrop.* 11(4): 559–575.

BICKEL, H. 1953. Cystine storage disease with aminoaciduria and dwarfism; Lignac-Fanconi disease. *Acta paediat.*, Upps. 42(6): 581–585.

BINDER, E., & BONSE, G. 1953. Über familiäre Haut- und Knochenhautverriesung. [Familial cutaneous and periosteal hypertrophy.] *Arch Derm. Syph.*, Berl. 196(2): 123–136.

BJORKLUND, S. I. 1953. Children of diabetic mothers; electrocardiographic studies in the newborn. *Acta paediat.*, Upps. 42(6): 526–534.

BLECHMANN, G. 1953. Évolution diverse d'une toxi-infection chez deuz jumeaux vrais. [Different evolution of a toxi-infection in two identical twins.] *Arch. fr. pediat.* 10(10): 1074–1075.

BÖÖK, J. A. 1953. A genetic and neuropsychiatric investigation of a North-Swedish population, with special regard to schizophrenia and mental deficiency. *Acta Genet.*, Basel 4(1): 1–100.

BORA, K. C. 1954. Delayed effects in chromosome breakage by X-rays. *Brit. J. Radiol.* 27(314): 124–127.

BRINKHOUS, K. M., & GRAHAM, J. B. 1954. Hemophilia and the hemophiloid states. *Blood*, Balt. 9(3): 254–257.

COLEMAN, E. N., & FOOTE, J. B. 1954. Cranio-stenosis with familial vitamin-D-resistant rickets. *Brit. M. J.* No. 4861: 561–562.

CROSBY, W. H., & AKEROYD, J. H. 1954. Some immunohematologic results of large transfusions of group O blood in recipients of other blood groups; a study of battle casualties in Korea. *Blood*, Balt. 9(3): 103–116.

CUMINGS, J. N. 1953. The cerebral lipids in disseminated sclerosis and in amaurotic family idiocy. *Brain*, Lond. 76(4): 551–562.

DAHLBERG, G. 1953. Notes on differentiated population increments. *Acta Genet.*, Basel 4(1): 101–117.

DE SPIRITO, A. 1953. Thrombocytopenic purpura in twins. *Clin. Proc. Child. Hosp.*, Wash. 9(12): 256–261.

DONOHUE, W. L., MULLINGER, M. A., COOK, E. G., & SNELLING, C. E. 1954. A survey of the Rh problem in Toronto, 1947–1952. *Am. J. Obst.* 67(2): 233–247.

ENGELFRIED, J. J. 1954. Ninety-six hundred blood transfusions without a serious reaction. *Am. J. Clin. Path.* 24(2): 247–249.

FILITTI-WURMSER, S., JACQUOT-ARMAND, Y., AUBEL-LESURE, G., & WURMSER, R. 1954. Physico-chemical study of human iso-haemagglutination. *Ann. Eugen.*, Lond. 18 (3): 183–202.

FITZPATRICK, T. B., & LERNER, A. B. 1954. Biochemical basis of human melanin pigmentation. *A. M. A. Arch. Derm. Syph.* 69(2): 133–149.

FOLLIS, R. H. JR. 1953. Histochemical studies on cartilage and bone. III. Osteogenesis imperfecta. *Bull. Johns Hopkins Hosp.* 93(6): 386–399.

FOY, H., KONDI, A., TIMMS, G. L., BRASS, W., & BUSHRA, F. 1954. The variability of sickle-cell rate in the tribes of Kenya and the Southern Sudan. *Brit. M. J.* No. 4857: 294–297.

GÉRARD-LEFEBVRE, M., MOLLET, F., LEFEBVRE, R., & BERNARD, F. 1953. Enquete sur le mongolisme dans le Nord de la France: essai d'étude étio-pathogénique. [Research on mongolism in North France; etiology and pathogenesis.] *Arch. fr. Pédiat.* 10(8): 834–854.

GIANFERRARI, L., CRESSERI, A., & MALTA-RELLO, A. 1954. Richerche sulla ereditarieta dell'idroftalmo e della cataratta congenita in paesi delle Prealpi Orobiche. [Studies on the inheritance of hydrophthalmos and of congenital cataract in villages of the Orobian foothills of the Alps.] *Acta genet. med. gemellol.*, Roma 3(1): 1–15.

GOLDSTEIN, H. 1954. A study of mongolism and non-mongoloid mental retardation in children. *Arch. Pediat.*, N. Y. 71(1): 11–28.

GOUDEMAND, M., & ROPARTZ, C. 1952–53. Répartition des génotypes Rh et des agglutinines irrégulieres anti-Rh dans le Nord de la France; étude sur 1,000 sujets et 65 sérums. [Distribution of Rh genotypes and irregular anti-Rh agglutinins in the Nord region of France; study of 1,000 subjects and 65 sera.] *Ann. Inst. Pasteur Lille* Vol. 5: 174–176.

GREBE, H. 1954. Familienbefunde bei letalen Anomalien der Korperform. [Familial findings in lethal anomalies of the human body.] *Acta genet. med. gemellol.*, Roma 3(1): 93–111.

GROVE-RASMUSSEN, M., & LEVINE, P. 1954. Occurrence of anti-D and anti-E in absence of obvious antigenic stimuli. *Am. J. Clin. Path.* 24(2): 145–149.

GUINET, P., PERRIN, J., MOUSSELON, J., & GARIN, J. P. 1953. Etude biologique et histologique d'un cas d'hermaphrodisme par ovo-testis. [Biological and histological study of a case of hermaphroditism by ovotestis.] *Ann. endocr.*, Par. 14(4): 623–627.

HARDY, L. H., RAND, G., & RITTLER, M. C. 1954. The H-R-R polychromatic plates. I. A. test for the detection, classification, and estimation of the degree of defective color vision. *A. M. A. Arch. Opth.* 51(2): 216–228.

HASÉK, M. 1953. Príspevek ke kritice morganistického výzkumu v lékarské genetice. [Critical considerations on Morganism in medical genetics.] *Čas. lék. česk.* 92: 1339–1346.

HAUGE, M., & HELWEG-LARSEN, H. F. 1954. Studies on linkage in man; red hair versus blood groups, P. T. C. and eye colour. *Ann. Eugen.*, Lond. 18(3): 175–182.

HOLLAENDER, A., & STAPLETON, G. E. 1954. Modification of radiation damage after exposure to x-rays. *Brit. J. Radiol.* 27(314): 117–121.

HOLT, S. B. 1954. Genetics of dermal ridges; bilateral asymmetry in finger ridge counts. *Ann. Eugen.*, Lond. 18(3): 211–231.

HOUEL, E., & ASSUS, A. 1953. Paradoxes au sujet de la maladie hemolytique du nouveau-ne. [Paradoxes concerning hemolytic disease of the newborn.] *Bull. Fed. soc. gyn. obst. fr.* 5: 432–433.

JACKSON, D. P., HARTMANN, H. C., & CONLEY, C. L. 1953. Clot retraction as a measure of platelet function. II. Clinical disorders associated with qualitative platelet defects (thrombocytopathic purpura). *Bull. Johns Hopkins Hosp.* 93(6): 370–385.

JELLIFFE, D. B., STUART, K. L., & WILLS, V. G. 1954. The sickle cell trait in Jamaica. *Blood*, Balt. 9(3): 144–152.

JONES, A. R. STEINBERG, A. G., ALLEN, F. H. JR., DIAMOND, L. K., & KRIETE, B. 1954. Observations on the new Rh agglutinin anti-f. *Blood*, Balt. 9(3): 117–122.

KALLMANN, F. J. 1954. Heredity and eugenics. *Am. J. Psychiat.* 110(7): 489–492.

KAPLAN, M., & BALDINO, C. 1953. Dysplasie périostale paraissant familiale et transmise suivant le mode mendelien recessif. [Periosteal dysplasia, apparently familial and transmitted according to the recessive Mendelian law.] *Arch. fr. pediat.* 10(9): 943–950.

KARN, M. N. 1954. Data of twins born in Italy 1936–1951. *Acta genet. med. gemellol.*, Roma 3(1): 42–49.

KATZENSTEIN, R., & RYAN, A. J. 1954. Exchange transfusion results in erythroblastotic infants. *Connecticut M. J.* 18(2): 210–215.

KLEINERT, H. 1953. Eine recessiv-geschlechtsgebundene Form der idiopathischen Netzhautspaltung bei nichtmyopen Jugendlichen. [A recessive sex-linked form of idiopathic retinal separation in non-myopic juveniles.] *Arch. Ophth.*, Munch. 154(3): 295–305.

KOLLER, F. 1954. Is hemophilia a nosologic entity? *Blood*, Balt. 9(3): 286–290.

LAMY, M., BERNARD, J., MALLARME, J., JAMMET, M. L., AUSSANNAIRE, M., & BADER, J. P. 1953. Anémie grave avec volumineuse splénomégalie et érythroblastose chez deux jumeaux monozygotiques: guérison par le traitement ferrique. [Severe anemia with voluminous splenomegaly and erythroblastosis in monozygotic twins: iron therapy.] *Arch. fr. pédiat.* 10(8): 871–874.

LAPIERE, S. 1953. Une série héréditaire et familiale de cas de maladie de Darier de type bulleux; un cas d'érythrodermie ichtyosiforme de type bulleux. [A hereditary and familial series of Darier's disease of bullous type; a case of ichthyosiform erythroderma of bullous type.] *Arch. belg. derm. syph.* 9(3): 249–253.

LAUGE-HANSEN, N. 1954. Fractures of the ankle. III. Genetic roentgenologic diagnosis of fractures of the ankle. *Am. J. Roentg.* 71(3): 456–471.

LAURENT, Y., & BROMBART, M. 1953. Un cas d'ostéochondrose disséquante observée chez deux frères. [A case of osteochondritis dissecans in two brothers.] *Acta orthop. belg.* 19(7): 322–329.

LEVER, W. F. 1953. Primary hypercholesteremic xanthomatosis and idiopathic hyperlipemia. *Bull. N. England M. Center* 15(4): 140–148.

LOW, D. M. 1954. The obstetrical management of the Rh-negative patient. *Am. J. Obst.* 67: 248–252.

LUDWIG, E. 1953. Hypotrichosis congenita hereditaria Typ. M. Unna. *Arch. Derm. Syph.*, Berl. 196(3): 261–278.

MCARTHUR, N. 1954. Changes in twin frequencies. *Acta genet. med. gemellol.*, Roma 3(1): 16–28.

MCARTHUR. N. 1954. The relative aetiological effects of maternal age and parity in binovular twinning. *Ann. Eugen.*, Lond. 18(3): 203–210.

MACFARLANE, W. V. 1953. Familial investigation in syphilis; a review of 670 families in whom the original patient suffered from a form of syphilis other than the acquired contagious type. *Brit. J. Vener. Dis.* 29(4): 203–209.

MACFARLANE, R. G. 1954. Hemophilia, Christmas disease, and matters of terminology. *Blood*, Balt. 9(3): 258–264.

MARANS, A. E., & KANOF, N. M. 1953. Congenital ectodermal defect of anhidrotic type in an infant. *Clin. Proc. Child. Hosp.*, Wash. 9(10): 225–228.

MERLE, M., & ROUHER, F. 1953. A propos deux cas d'angiomatose kystique rétinienne dans la méme famille. [Two cases of retinal cystic angiomatosis in the same family.] *Bull. soc. opht. France* No. 6: 637–642.

MINNICH, V., NA-NAKORN, S., CHONG-CHAPEONSUK, S., & KOCHASENI, S. 1954. Mediterranean anemia; a study of thirty-two cases in Thailand. *Blood*, Balt. 9(1): 1–23.

MORRIS, J. V., & MACGILLIVRAY, R. C. 1954. Multiple mongolism in a family. *Brit. M. J.* No. 4863: 687.

MOTULSKY, A. G., SINGER, K., CROSBY, W. H., & SMITH, V. 1954. The life span of the elliptocyte; hereditary elliptocytosis and its relationship to other familial hemolytic diseases. *Blood*, Balt. 9(1): 57–72.

NAYRAC, P., FONTAN, M., WAROT, P., & LORRAIN, A. 1953. L'hérédo-ataxie cérébelleuse de Pierre Marie; a propos d'une observation familiale. [Pierre Marie's hereditary cerebellar ataxia; familial observation.] *Écho méd. nord* 24 (8–9): 279–284.

NAYRAC, P., & WAROT, P. 1953. Les hérédo-dégénérescences spino-cérébelleuses. [Hereditary spino-cerebellar degeneration.] *Écho méd. nord* 24(8–9): 263–265.

NAYRAC, P., & WAROT, P. 1953. Paraplégie spasmodique familiale chez deux soeurs. [Familial spasmodic paraplegia in two sisters.] *Écho méd. nord* 24(8–9): 266–269.

PAVLOVSKY, A. 1954. Present concepts of hemophilia. *Blood*, Balt. 9(3): 291–293.

PETSCHELT, E. 1953. Zur Klinik, Symptomatologie, Lokalisation, Alters- und Geschlechtsverteilung des Naevus vasculosus osteohypertrophicus (Klippel-Trenaunay-Parkes-Webersches Syndrom). [Pathology, symptomology, localization, age, and sex distribution in naevus vasculosus ostoe-hypertrophicus (Klippel-Trenaunay-Parkes-Weber syndrome).] *Arch. Derm. Syph.*, Berl. 196 (2): 155–169.

PIRNER, F., & BORELLI, S. 1953. Beitrag zum Hermaphroditismus verus. [Report on true hermaph-roditism.] *Arch. Derm. Syph.*, Berl. 196(4): 329–355.

PLANQUES, J., RUFFIE, J., & DUCOS, J. 1953. Sur un cas d'exclusion de filiation en l'absence de la mere. [Exclusion of paternity in the absence of the mother.] *Ann. med. leg.* 33: 167–169.

PROCHÁZKA, J., & HNĚVKOVSKÝ, O. 1953. Degenerační kloubni změny u alkaptonurie a jejich vztah k problému etiologie arthros. [Degenerative articular changes in alkaptonuria and their role in the problem of etiology of arthroses.] *Acta chir. orthrop. traum. čech.* 20(3): 53–59.

PROKOP, O., WICHMANN, D., & GELLER, W. 1953. Die Verteilung der Rh-Untergruppen bei An-staltskranken. [Distribution of Rh-subgroups in patients in mental institutions.] *Arch. Psychiat.*, Berl. 190(6): 562–566.

QUICK, A. J. 1954. On the nature and diagnosis of hemophilia. *Blood*, Balt. 9(3): 265–272.

ROBERTS, D. F. 1953. Body weight, race and climate. *Am. J. Phys. Anthrop.* 11(4): 533–558.

ROCHE, J., DERRIEN, Y., & ROQUES, M. 1953. Sur le remplacement des hémoglobines de type adulte par celles de type foetal au cours du developpement embryonnaire et après la naissance, chez l'homme et chez le boeuf. [The replacement of fetal type hemoglobins by adult types during embryonic development and after birth, in man and in cattle.] *Bull. Soc. chim. biol.*, Par. 35(8): 933–943.

ROHMER, P., SCHNEEGANS, E., ROEDERER, J., & HAARSCHER, A. 1953. Epidermolyse bulleuse congénitale et familiale. [Congenital and familial epidermolysis bullosa.] *Arch. fr. pédiat.* 10(8): 828–833.

RÜDIN, E. 1953. Ein Beitrag zur Frage der Zwangskrankheit, insbesondere ihrer hereditären Bezie-hungen. [On the problem of compulsive disease with special reference to its hereditary relations.] *Arch. Psychiat.*, Berl. 191(1): 14–54.

RUFFIE, J., & HURON, R. 1953. Nouvelle methode de calcul de la probabilite d'exclusion de paternite. [A new calculation method of excluding paternity.] *Ann. med. leg.* 33: 164–167.

RUZICSKA, G. 1953. The significance of developmental anomalies of ova in the aetiology of abortions. *Acta morph. hung.* 3(3): 255–273.

SACHS, L. Sex-linkage and the sex chromosomes in man. *Ann. Eugen.*, Lond. 18(3): 255–261.

SANZ MUNOZ, M. 1953. Algunos aspectos de la genética en bioquimica. [Biochemical problems in genetics.] *An. Acad. farn.*, Madr. 19(3): 195–216.

SAVAGE, C. R. 1954. Familial intestinal polyposis with pigmentation of the face, lips, mouth and digits. *Brit. J. Surg.* 41(168): 366–367.

SCHIER, W. W. 1954. Familial Hodgkin's disease. *Blood*, Balt. 9(3): 236–240.

SCHULMAN, I., & SMITH, C. H. 1954. Fetal and adult hemoglobins in hemolytic disease of the new-born. *A. M. A. Am. J. Dis. Child.* 87(2): 167–178.

SPINK, W. W. 1954. Family studies on brucellosis. *Am. J. M. Sc.* 227(2): 128–133.

STECHER, R. M. 1954. Heberden's nodes: concordant osteoarthritis of the fingers in identical twins. *Acta genet. med. gemellol.*, Roma 3(1): 84–92.

STEFANINI, M. 1954. Hemophilia: specific entity or syndrome. *Blood*, Balt. 9(3): 273–280.

TILLNER, I. 1954. Ueber die Vierfingerfurche und ihre Uebergansformen, insbesondere bei Zwillingen. [The simian line and its transitional forms, particularly in twins.] *Acta genet. med gemellol.*, Roma 3(1): 50–83.

TOCANTINS, L. M. Hemophilic syndromes and hemophilia. *Blood*, Balt. 9(3): 281–285.

TYLER, F. H., & STEPHENS, F. E. 1954. Methods of investigation of human inheritance. *Bull. M. Libr. Ass.* 42(1): 3–9.

VENNING, P. 1954. Sib correlations with respect to the number of phalanges on the fifth toe. *Ann. Eugen.*, Lond. 18(3): 232–254.

WAHL, C. W. 1954. Some antecedent factors in the family histories of 392 schizophrenics. *Am. J. Psychiat.* 110(9): 668–676.

WATSON, H. B., CROSSE, V. M., & HATCHUEL, W. L. 1954. Premature delivery in haemolytic disease of newborn. *Brit. M. J.* No. 4863: 679–680.

WIENER, A. S., GORDON, E. B., & COHEN, L. 1954. Studies on the heredity of the human blood groups. II. The A-B-O groups. *Acta genet. med. gemellol.*, Roma 3(1): 29–33.

WILDERVANCK, L. S. 1954. A deaf-mute and a "hearing-mute" uniovular twin. *Acta genet. med. gemellol.*, Roma 3(1): 34–41.